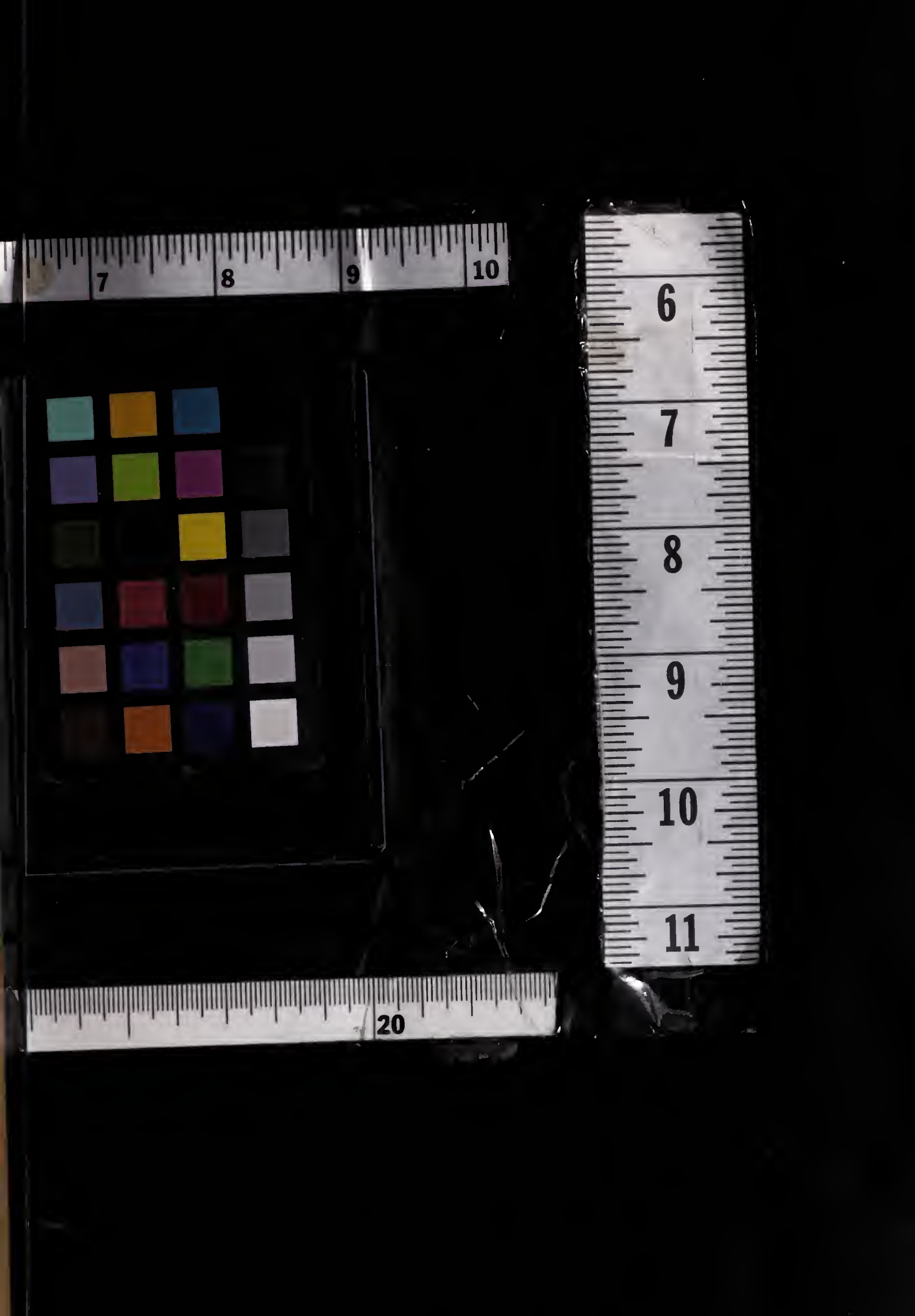

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BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

ORGANO OFICIAL



VOL. 60 ENERO A DICIEMBRE DE 1968 NUMS. 1-12

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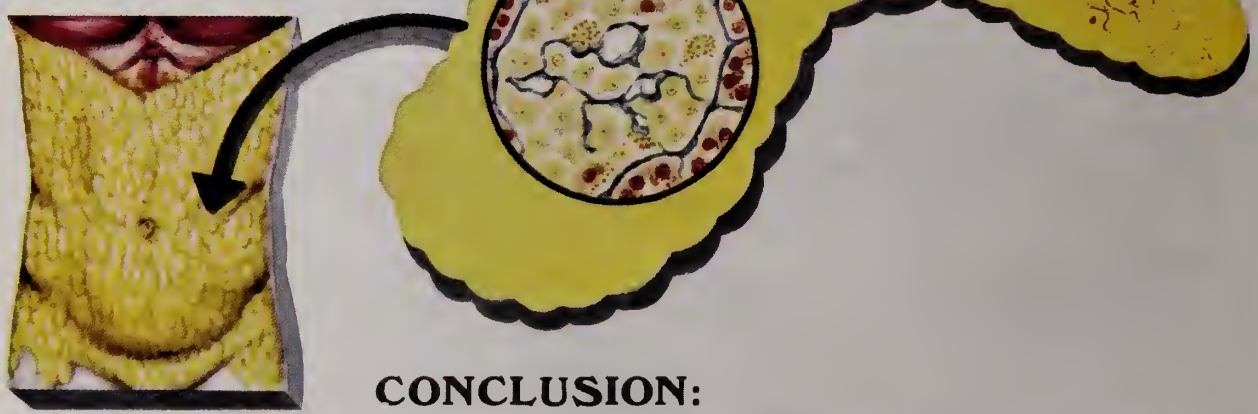
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DBI-TD Does Differ From the Sulfonylureas

SULFONYLUREAS stimulate insulin release by the pancreatic beta cells. Endogenous insulin is often present in excess in stable adult diabetics who are overweight.[1,2] This insulin is apparently inefficient in transporting glucose into skeletal muscle, although it retains its activity in adipose tissue.[3,4] Insulin is not only a potent lipogenic hormone, it is also antilipolytic (suppresses fat mobilization from tissues) and thus can contribute to weight gain.

DBI-TD

DBI-TD, on the other hand, acts independently of the pancreas to promote increased glucose utilization in skeletal muscle.[6,7] DBI-TD increases the entry of glucose into muscle cells, possibly by facilitating the action of insulin on muscle; it does not increase glucose uptake by the fat cells or prevent them from releasing fatty acids and glycerol. Thus, in the overweight stable adult diabetic who often releases excessive endogenous insulin in response to hyperglycemia, DBI-TD supplements the insulin action and may compensate for its physiologic inefficiency in this regard.[4,6,7]

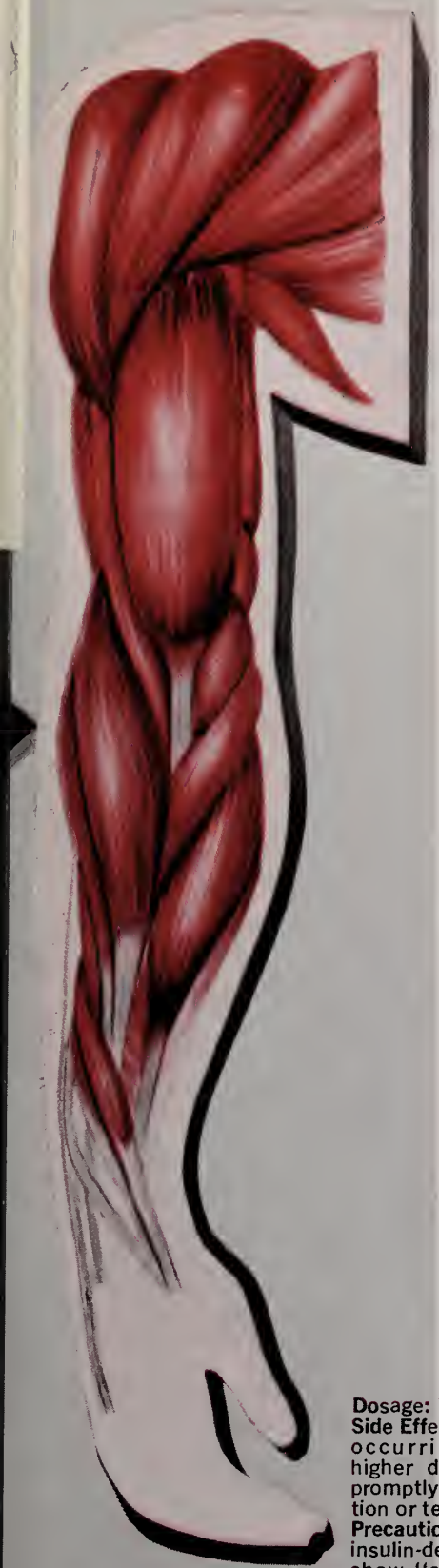


CONCLUSION:

DBI-TD acts directly to enhance muscle glucose utilization, whereas sulfonylureas appear to depend upon a supply of insulin releasable from the patient's pancreas for their hypoglycemic effect. Unlike injected insulin or the endogenous insulin released under the stimulus of the sulfonylureas, DBI-TD does not promote the conversion of glucose to fat or prevent the mobilization of fatty acids from the adipose tissue depots of the body.

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- Promotes gradual weight loss*

*Although anorexia has been suggested as a possible basis for weight loss, controlled studies do not support this. In nondiabetic subjects who are overweight, comparable doses of DBI-TD do not induce weight loss or lower blood sugar.

Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis (acetonuria without hyperglycemia) which must be differentiated from "insulin lack" ketosis which is accompanied by acidosis, and treated accordingly. Lactic acidosis has been reported in nondiabetics and diabetics treated with insulin, with diet, and with DBI. Question has arisen regarding possible contribution of DBI to lactic acidosis in patients with renal impairment and azotemia and also those with severe hypotension secondary to myocardial or bowel infarction. Periodic B.U.N. determination should be made when DBI is administered in the presence of chronic renal disease. DBI should not be used when there is significant azotemia. Any cardiovascular lesion that could result in severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also available:** DBI tablets 25 mg. Consult product brochure.

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Actions: Vibramycin (doxycycline), a new broad-spectrum antibiotic, differs from other tetracyclines in its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage. Also, in comparison with certain other tetracyclines, the absorption of Vibramycin is not notably diminished by the ingestion of food or milk.

After discontinuance of therapy, effective antibacterial levels of Vibramycin are usually present for 24-36 hours.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin has been found to be clinically effective in the treatment of a variety of bacterial infections of the respiratory and genitourinary tracts and soft-tissue infections. Since Vibramycin is a member of the tetracycline series, it may be expected to be useful in the treatment of gastrointestinal, ophthalmic and other miscellaneous infections when caused by susceptible organisms.

Contraindications: Vibramycin is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: In patients with impaired renal function, reduce usual oral dosage and consider serum level determinations to avoid liver damage from excessive systemic accumulation.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although in vitro it binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving tetracyclines, which effect disappears rapidly on cessation of therapy.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy, as with other antibiotics. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended.

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections, up to 2 mg./lb. of body weight may be used. For children over 100 lbs., the usual adult dose should be used. Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present for 24 to 36 hours following the discontinuation of Vibramycin.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Aluminum hydroxide gel given with tetracycline antibiotics has been shown to decrease their absorption.

Supply: Vibramycin Hyclate (doxycycline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline, bottles of 50.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing when reconstituted doxycycline monohydrate equivalent to 25 mg. of doxycycline per 5 cc. (each teaspoonful), with a pleasant-tasting raspberry flavor, 2 oz. bottles.

More detailed professional information available on request.

Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.



Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when Tofrānil was added to the regimen.
Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (includ-

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In about 3 out of 4 cases, Tofrānil relieves symptoms of primary depression.

As maintenance therapy in primary depressive illness, it helps prevent relapse.

Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, in patients with cardiovascular disease, thyroid disorders, increased intraocular pressure, or in those receiving anticholinergics (including antiparkinsonism agents), the special precautions listed in the Prescribing Information should be carefully observed. The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

Tofrānil® imipramine hydrochloride Geigy

ing hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Tofrānil: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
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BLOOD PRESSURE AND CHOLESTEROL LEVELS IN PUERTO RICAN GROUPS

III. Hospital Visitors, Rural Dwellers, and Urban Dwellers

Raúl Costas, Jr., MD
M. R. García Palmieri, MD
Manuel Feliberti, MD
Herbert Benson, MD
A. A. Colón, MD
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During the past few years the authors have been engaged in a series of research studies as an outcome of which, information on blood pressure and serum cholesterol levels among various Puerto Ricans populations has been obtained. In a previous communication (1) data on patients with atherosclerotic heart disease, their relatives, a group of normal controls, and their relatives have been presented. In a second publication (2) a similar comparison was made between industrial workers, mountain dwellers, and coastal dwellers. These various groups studied, necessarily small due to limitations of time and facilities, have shown some differences in blood pressure and serum cholesterol values, but not to the extent of attaining statistical significance.

The present paper is concerned with a similar study of four other groups. Although the numbers are still small, the degree of significance has been increased by sampling two of the groups from two small communities, so that the sample taken represents as close to 100% as possible of the age and sex groups studied.

From the Department of Medicine of the University of Puerto Rico School of Medicine. *This study was supported by Contract No. PH-43-63-620, from the Division of Collaborative Studies of the National Heart Institute of the U. S. Public Health Service.*

Materials and Methods

All four groups were composed of males aged 45 to 64 years.

The groups of the hospital visitors were drawn from men of the specified ages visiting hospitalized patients in the University Hospital during a period of two months. All male visitors were approached personally as they walked into the hospital during visiting hours, and those of the appropriate age groups were asked to participate in the study. An appointment for examination was then given. An estimated 90% of individuals approached agreed to the examination, but only about 75% of these could be eventually examined. They were separated into two groups: one residing mainly in city areas comprising the communities of Bayamón, Carolina, Guaynabo and Cataño; and another group residing primarily in the country, as represented by the communities of Aguas Buenas, Comerio, Corozal, Cidra, Barranquitas and Naranjito. For administrative reasons residents of San Juan, Santurce and Rio Piedras were excluded. Because of the method of selection the groups are weighed with "publico" drivers and clergymen.

Rural dwellers were taken from Barrio Palmarito near Corozal. Palmarito is in the mountains and had been classified as an isolated community until three months prior to the study. It is thoroughly rural, some of the inhabitants never having visited the town. The sample includes all but one of Palmarito's males aged 45 to 64.

The group of urban dwellers was obtained at

The two groups of hospital visitors were constructed by arbitrarily calling some areas urban and other rural, assuming that the characteristics of the inhabitants would be uniform for each area. It seems obvious that this assumption is incorrect, and that there is a mixture of individuals with different characteristics, for country and for city, in each area. This was initially suggested by the actual numerical values obtained for the two parameters in the four groups. Figures for the groups of hospital visitors were not only intermediate between the urban and rural dwellers, but they seemed to be near the averages of the extreme values. This was tested by combining the urban and rural groups and comparing the averages with those of the intermediate groups. As shown in Table V the differences disappear; the values are now nearly the same.

TABLE V: COMPARISON OF OVER-ALL MEAN VALUES, URBAN AND RURAL DWELLERS GROUPED TOGETHER

	Hospital Visitors Group A	Hospital Visitors Group B	Urban and Rural Dwellers Combined
Blood Pressure	138/81	137/81	134/82
Serum Choresterol	216	220	216

It seems then that one way of obtaining groups which are really different in the characteristics studied here is to carry out the sampling in areas which by actual inspection have been found to be definitely rural or definitely urban. Since the differences are statiscally significant ($p<0.02$), it is probable that they reflect a real difference in these parameters. This should be borne in mind by investigators conducting epidemiological studies of cardiovascular disease.

Summary

One hundred sixty-nine hospital visitors from city areas, 130 from country areas, 52 urban dwellers, and 44 rural dwellers had blood pressure and serum cholesterol determinations. All were males between the ages of 45 and 64 years.

Urban dwellers had the highest blood pressure and cholesterol levels, rural dwellers the lowest, and both groups of hospital visitors intermediate and similar levels. Differences in both parameters between urban and rural dwellers were statistically significant.

A possible explanation of the intermediate values of the hospital visitors, as well as of the failure to obtain statistically significant differences in groups studied previously, is presented briefly.

The importance of these findings to investigators in this field is stressed.

Resumen

Se determinó la tensión arterial y el colesterol sérico en 299 personas que visitaron enfermos en el Hospital Universitario, en 52 residentes de zona urbana y en 44 de zona rural. Los 299 visitantes se subdividieron en dos grupos, uno de 169 habitantes de la ciudad y otro de 130 habitantes del campo. Todos eran varones entre 45 y 64 años de edad.

Los residentes de zona urbana registraron los valores de tensión arterial y colesterol más altos, y los de la zona rural, los más bajos; mientras que los dos grupos de visitantes mostraron valores intermedios y similares entre sí. Las diferencias de ambos parametros entre los grupos de residentes urbanos

y rurales alcanzaron significación estadística.

Se postula una teoría que explica los valores intermedios en los grupos visitantes, así como la dificultad de obtener diferencias significativas en otros grupos estudiados anteriormente.

Se menciona el interés de estos hallazgos para otros investigadores en el mismo campo.

Acknowledgement

We are indebted to Mrs. Norma Feliberti and Mrs. Ileana Fullana for technical assistance; to Mr. Jaime López for statistical work; to Dr. William Zukel and Mr. Harold Kahn from the Division of Collaborative Studies of the National Heart Institute, and Dr. William B. Kannel from the Framingham Study, for their supervision and advice, without which this study could not have been accomplished.

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TRANSABDOMINAL AMNIOCENTESIS
Evaluation of a Procedure

Stanley H. Asensio, MD
Iván A. Pelegrina, MD

The introdution of a needle into the amniotic sac dates as far back as 1930 when Menees, Miller and Holly (1) reported the procedure of introducing a radiopaque medium into the amniotic cavity with the purpose of opacifying the sac for the better visualization of the placenta. The procedure did not gain popularity and was discontinued, probably due to irritating properties of the inorganic iodide compound. Sporadic reports on amniocentesis have been published since then (2, 3).

During the last few years we have witnessed an increasing interest in the amniotic sac, amniotic fluid and the developing fetus. Acute hydramnios is treated with repeated amniocentesis or by implantation of indwelling catheters in the amniotic sac with continuous removal of fluid (4). Pregnancy, after the diagnosis of fetal death in utero, is terminated by the intrauterine injection of hypertonic glucose solution or hypertonic saline solution (5). The amniotic fluid spectrophotometric scanning in the diagnosis of erythroblastosis fetalis has become an accepted routine obstetrical procedure (6-10). The injection of a radiopaque medium into the amniotic cavity with the purpose of visualizing the placenta is a tool in the diagnosis of placenta previa (1, 3, 11), and hydatidiform mole (12).

Amniocentesis, either with the idea of diagnosing erythroblastosis fetalis, treatment of acute hydramnios, amniographic studies, or termination of pregnancy has become a world wide accepted obstetrical procedure. It is said to be a safe procedure for mother and fetus and the information obtained through it may be life saving.

In spite of encouraging reports from all over the world, transabdominal amniocentesis is practiced by very few obstetricians in Puerto Rico. It is our purpose to report our experience with 500 cases.

Materials and Methods

All patients studied belong either to the Obstetrical and Gynecological Department of the Sshool of Medicine of the University of Puerto Rico or the private practice of the authors.

The procedure is explained to the patient and she is advised to empty her urinary bladder. She is reclined on the examining table and her abdomen examined for presentation and position of the fetus. The operator proceeds with surgical cleansing of the patient's abdomen with alcoholic zephiran. The abdomen is drapped with sterile material and fetal parts rechecked to obtain a good "target" area from where to obtain amniotic fluid, where to inject hypertonic solutions, or where to inject radiopaque material if amniography is contemplated. In patients near term with the presenting part engaged, the best place for amniotic sac puncture is among the small parts or close to the neck of

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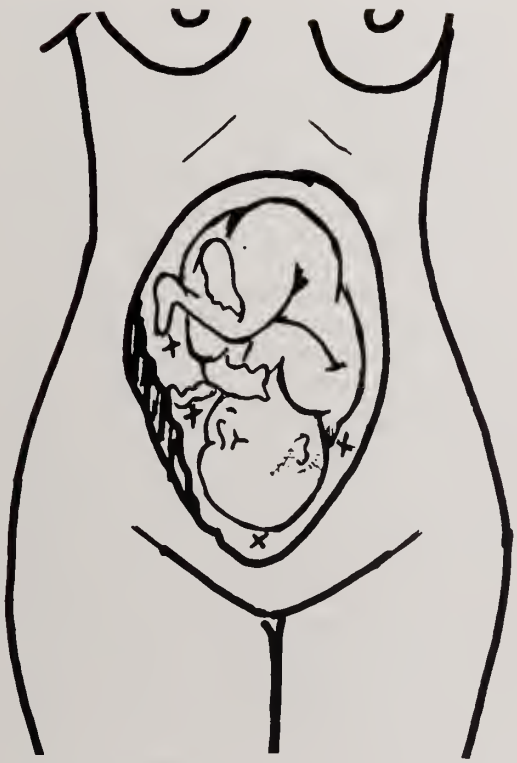


Fig. 1: Preferred "target" areas for amniocentesis indicated by X.

the fetus. When the presenting part can be lifted up the lower uterine segment offers a safe "target" area (Fig. 1). Once the "target" area is decided on, 5 cc of 1% Lidocaine solution is injected all the way to the fascia and parietal peritoneum. A 3 1/2 inches gauge 22 spinal needle (gauge 18 in case of amniography) is then introduced into the amniotic sac, the stylus removed, and free flowing amniotic fluid obtained. When the procedure is over, the stylus is reinserted and the needle removed. The puncture area is covered with collodium. Patients are followed with vital signs, fetal heart tones and observed for evidence of infection. They are instructed to report any signs or symptoms out of the ordinary.

Results

The indications for the 500 amniocentesis were those on Table I. The procedure was performed in patients with pregnancies as early as 20 weeks. No attempts have been made to perform amniocentesis in pregnancies earlier than 20 weeks. There were patients that had one amniocentesis and others had as many as 32. The average was 2 amniocentesis to a patient. Complications that may occur are listed in Table II.

TABLE I: INDICATION FOR AMNIOCENTESIS

Indication	No.
Amniotic fluid bilirubin scanning	292
Amniography	200
1. Suspected fetal edema	60
2. Localization of the placenta	60
3. To rule out monoamniotic twins	40
4. To rule out congenital fetal anomaly	23
5. To rule out fetal death	5
6. To diagnose hydatidiform mole	5
7. To diagnose uterine anomalies	3
8. To study fetal distress	4
Termination of pregnancy	6
Treatment of acute hydramnios	2
Total	500

TABLE II: POSSIBLE COMPLICATIONS

Pain in the area of puncture
Sepsis or morbidity
Premature rupture of the membranes
Premature labor
Abruptio placenta
Increased Rh sensitization
Puncture of fetal part
Allergic reaction
Failure to obtain amniotic fluid

The most common complaint was pain in the area of puncture. This was present most commonly when the injected site was the

suprapubic region. The complaint is most difficult to evaluate since pregnant patients usually complain of abdominal aches, most frequently a suprapubic distress due to pressure of the fetus on the area.

One case with intrauterine fetal death to which hypertonic glucose in water was injected as a means of termination of pregnancy, had severe intrauterine infection. No other case showed evidence of local infection, sepsis, endometritis or morbidity.

Patients with twin pregnancy and patients with placenta previa in whom amniocentesis was performed with the sole purpose of obtaining amniotic fluid failed to go into premature labor but 10% of cases of twin pregnancy did go into labor within 48 hours after injection of contrast medium. Only two cases who had amniocentesis for determination of Rh sensitization ruptured membranes few minutes after the procedure. Both cases were 34 weeks pregnant and the procedure was done in the lower uterine segment.

The problem of puncturing a placental blood vessel or breaking placental villi resulting in a premature separation of the placenta is more theoretical than real. In our cases no pains were taken to localize the placenta prior to the amniocentesis. Even in cases of suspected placenta previa with floating presenting part the target area for amniocentesis was the lower uterine segment. We think that if the needle is introduced without moving it up and down, the placenta is pierced cleanly. No case where amniocentesis or amniography was done showed increased vaginal bleeding or increased incidence of abruptio placenta. No case of fetal anemia resulted from the procedure.

Some articles (13) report increased maternal antibody titer after amniocentesis, if fetal bleeding into the maternal circulation takes place. This may be so, but usually, the bleeding (if any) takes place into the amniotic cavity and not into the maternal circulation. Of the 290 amniocentesis done on Rh sensitized mothers, only five showed an increase of one tube titer. The case receiving 32 amniocentesis failed to show increased Rh titers ascribable to the procedure.

If the procedure is done carefully and as described, fetal parts will not be punctured. The fetus, if touched, will move away from the needle point. If no amniotic fluid is obtained upon aspiration, we have to suspect fetal puncture. The needle should be retracted until free flowing fluid is obtained. No radiopaque material should ever be injected unless free flowing amniotic fluid is obtained by aspiration after every five ml of injected dye. One fetus received 10 ml of injected dye in the buttock resulting in a bleb. This was treated as a second degree burn after birth and healed well.

When the patient has a small uterus and is obese, or when the fetus is large and the amount of amniotic fluid is decreased, failure to obtain amniotic fluid may occur. When free flowing amniotic fluid is not obtained, we have to assume that the needle point is either in the uterine wall or the fetus. Careful reinsertion or retraction may correct it. This failure occurred in 20 cases, more commonly when the amniocentesis was performed not in the lower uterine segment. When the presenting part was disengaged and the target area was the suprapubic region fluid was always obtained.

Discussion

Transabdominal amniocentesis was performed in 500 cases. At the beginning the procedure was carried out in the operating

room. Later on it was moved to the procedure room, and lastly carried out in the outpatient clinic or X-ray table. We have seen no difference in the complications by so doing. No antibiotics have ever been introduced into the amniotic cavity or given to the patient during or after the procedure. Previous abdominal surgery has not been considered a contraindication for amniocentesis, this being performed in cases with previous cesarean section scars, appendectomy, exploratory laparotomy, and inferior vena cava ligation. Maternal diseases are no contraindication to amniocentesis, this having been performed in the past in patients with diabetes, toxemia, anemia, heart disease and hepatitis. *No case should ever be tried in a patient with skin disease.*

Some authors advocate the opening of the skin with a scalpel and introducing the needle through the incision as a means of decreasing skin bacteria from being carried into the amniotic sac. We have never done this and have had no morbidity.

No complications were produced by the procedure other than slight pain in the area of injection which disappeared in few hours. In the two cases who had amniotic fluid leakage after amniocentesis the procedure was carried out in the lower uterine segment, and the uterus was probably pushed up at the time of displacement of the presenting part, so that the amniotic sac puncture was carried out almost at the internal cervical os. Since then, we have been careful in pushing up the presenting part alone and the episode has not repeated.

Once case of infection of amniotic sac secondary to hypertonic glucose in water injection as means of inducing labor in a patient with dead fetus, shows not that the procedure should be discontinued, but that other hypertonic solutions are safer than glucose in water.

The increased incidence of premature rupture of the membranes in cases of multiple pregnancy and placenta previa when contrast medium is injected suggests reevaluation of amniography in these conditions.

We do not pretend to propose that there are no risks when a needle is introduced in the amniotic cavity, since all medical procedures always carry some danger with them, but we think that when the information to be obtained by this procedure outweights the minimal risks produced, it should be used. The procedure is a simple one, the instruments needed are available at all hospitals, the complications in expert hands are nil and the patient has much to gain.

Summary

Results of 500 transabdominal amniocentesis done at the Obstetrical and Gynecological Service of the University Hospital are reported. Indications and contraindications are discussed. The procedure is a simple one, the materials needed are available at all medical offices and hospitals, the complications are negligible and the information obtained invaluable in the better diagnosis and treatment of obstetrical patients.

Resumen

Se informan los resultados de 500 amniocentesis transabdominales efectuadas en pacientes del Servicio de Obstetricia y Ginecología del Hospital Universitario. Se discuten sus indicaciones y contraindicaciones. El procedimiento es sencillo, los materiales

requeridos se encuentran disponibles en hospitales y oficinas médicas, las complicaciones son mínimas y la información obtenida es de inmenso valor en el mejor tratamiento del paciente obstétrico.

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REPAIR OF THE DISRUPTED FLEXOR MECHANISM OF THE HAND

E. Blas Ferraiouli, MD, FACS, DABS

Surgery of the hand is usually concerned with laceration of tendons and very frequently with the repair of the flexor mechanism. In this era of warfare and mechanization, injury to the hand is a frequent occurrence. In Puerto Rico, hand injuries head the list of industrial accidents involving the upper extremity and are responsible for a large proportion of compensation and medical expenses (Table I). From the socio-economic standpoint, the function of the hand is of vital importance to the manual worker. It is the responsibility and aim of the hand surgeon to restore this function as perfectly as possible, to return the patient to wage-earning and self support. Strict adherence to the principles of tendon repair and good technique will usually give satisfactory results.

TABLE I: NUMBER AND ECONOMIC LOSS FROM HAND INJURIES

Year	Agriculture Laborers	Agriculture Injuries	Construction Laborers	Construction Injuries	Hand Injuries Total No.	Economic Loss Man-Hours	Compensation $ Paid
1961	48,000	2,123	49,000	839	3,062	$ 2,869,312	$ 398,719
1962	45,000	2,344	53,000	1,020	3,364	3,724,406	542,818
1963	40,000	2,370	62,000	1,043	3,413	5,601,456	523,959
1964	32,000	2,374	65,000	1,183	3,557	6,605,968	649,819
Total	165,000	9,611	229,000	4,185	13,396	18,800,878	2,115;315

Statistics provided by the Department of Labor, Commonwealth of Puerto Rico.

Note: In spite of the increase *in the labor force in the construction industry as compared to the* decrease *in labor force in agriculture, the total number of injuries of the hand remains higher in agriculture at a ratio of 2.34 to 1.*

The *first-aid care* of the wounds of the hand is directed primarily at protection. It should provide protection from infection and added injury, disability and deformity (1). After soft tissues, tendons and nerves have sloughed and the storm of infection is over, all the tissues contract resulting in flexion contractures and the mobile joints become bound with cicatrix into a frozen hand. Much of this disability can be spared by correct early treatment of hand injuries. The best first-aid consists in the application of a sterile dressing, a firm compression bandage and immobilization with splints in

From the Surgical Service, San Juan Veterans Hospital and the Puerto Rico State Insurance Fund.

the position of function. No attempt should be made to examine, clean or treat the wound until operating room facilities are available.

After definite appraisal of the structural damage, *definitive treatment* in a well-equipped operating room with good lighting — adequate instruments, complete anesthesia (general or axillary block) and a completely bloodless field— is mandatory. Following the anesthetization of the patient a pneumatic inflated cuff tourniquet up to 250 mm Hg is used after the blood has been drained with the use of an elastic bandage. Tender cleansing of the wound area, and entire forearm with soap and water, removing all foreign material and repeated cleansing of the wound by irrigation with warm normal saline solution, should be made. No attempt to suture the tendon structures should be done if the wound is grossly contaminated or the time elapsed since the injury is more than twenty-four hours. In such a case, the wound is carefully sutured and the divided digital nerves are approximated with 7-0 eye silk sutures. The hand is immobilized in position of function and tetanus toxoid or antitoxin (Hypertet®) given as indicated.

Following the primary healing, the interphalangeal joints and metacarpophalangeal joints are mobilized thru a full functional range by diligent passive exercises.

A *secondary repair* can be made as soon after induration has subsided and the interphalangeal joints are mobile, usually averaging four to six weeks.

Primary Principles

No primary suturing of the tendons is done when both sublimis and profundus tendons are divided in the area between the proximal interphalangeal joints and the distal palmar crease (No man's land). The skin is sutured and the digital nerves are approximated if both are involved to be followed by secondary tendon graft (2).

When the profundus tendon is divided near its insertion and the sublimis is intact primary repair is indicated.

In order to identify the flexor tendons involved in the palm and wrist without disturbing the wound dressing the following test is of great help:

Ferraiouli's Compression Test

The injured hand is grasped by the examiner at the wrist level (Fig. 1) by



Fig. 1: Flexor compression test: a) normal reaction (negative), b) laceration 2-3-4th fingers (positive).

placing the thumbs on the dorsal surface and the fingers opposing in the volar surface. By compressing the flexor tendons against the pronator quadratus and bony structures in a normal hand, there is an active flexion of the fingers (negative reaction); in a wounded hand there is no active flexion of the digits (positive reaction).

Tendon Grafts

The grafts can be obtained from the palmaris longus (this is absent in 5% of patients); next from the extensor digitorum communis of foot, the divided flexor sublimis tendon, and plantaris tendon. The graft should be anchored proximally to the profundus tendon at the level of the lumbricalis muscle and sutured distally to the end stump of the profundus tendon at the terminal phalanx by an end-to-end suture, or secured with a Bunnell pull-out wire into the bone cortex using a No. 34 monofilament stainless steel wire.

In children end-to-end sutures are made both proximally and distally and no pull-out wire sutures are used. The hand is immobilized in the neutral position, including the affected fingers only.

Dr. William Littler (2) has very well pointed out the importance of lacerations or wounds at the *enemy territory;* that is, a wound involving the division of tendons at the flexor compartment of the wrist. An injury at this level with division of both median and ulnar nerves, both ulnar and radial arteries and the digital flexor tendons, is considered a physiological and functional loss of the hand. When this happens the hand becomes ischemic, there is loss of sensation, the intrinsic muscles are paralyzed, and there is loss of flexion of all interphalangeal and metacarpophalangeal joints. If too much surgery is attempted at the flexor compartment of the wrist, all the structures will be consolidated by a mass of scars, and potential re-inervation and tendon amplitude will be greatly reduced. Here it is important to concentrate on the prime functional element and the structures should be repaired accordingly:

a. The median and ulnar nerves.
b. The flexor pollicis longus.
c. The index profundus tendon.
d. The common flexor profundus tendon, to the middle, ring and little fingers.
e. The middle and ring sublimis finger tendons.

An area of antibrachial fascia should be excised at this level to provide greater freedom of tendon structures. *The wrist flexors are not sutured* (6).

After Care

The extremity is kept elevated for the first 4 days. Antibiotics are administered systematically. The cast and sutures are removed in 4 weeks. When nerves have been divided, corrective dynamic splints are applied until re-inervation of the paralyzed muscles has occurred. Active exercises and adequate occupational therapy are provided.

Material

Fifty-seven cases from 1951-1962 involving the flexor tendon mechanism were reviewed. All cases were treated with secondary tendon grafts and were operated by the author. The injuries usually involved more than one finger: 21 the middle and ring fingers; 10 the index and middle fingers; 12 the little finger; 8 the thumb; 3 the index finger; 3 the index, middle and ring fingers. (Table II)

TABLE II: NUMBER OF TENDONS GRAFTS (94)

No.	Fingers Involved
21	middle & ring
10	index & middle
12	little
8	thumb
3	index
3	index — middle — ring

Results

Results (Table III) were classified using Boyes' classification: *excellent*—patients who were able to touch the distal palmar crease flexing the finger; *good*— patients who were able to flex to within ½ inch of the distal crease; *fair*— patients who were able to flex to within 1 inch of the distal crease, and patients who were able to flex to within 1½ inches of the distal palmar crease.

TABLE III: RESULTS

Cases (57)

No.	Results (Boyes Classification)
15	excellent
25	good — ½"
12	fair — 1"
5	poor — 1½"



Fig. 2: J. N. G., accident in 1949, age 7. Flexor tendon graft 4th finger on july 1958.



Fig. 3: F. T. R., age 38. Flexor tendon graft 5th finger.

Cases were considered inoperable when there was extensive cicatrix present, and poor mobilization of the metacarpophalangeal and interphalangeal joints.



Fig 4: R. R. F., age 32. Flexor tendon graft, 3rd finger.





Fig. 5: M. R. R., age 41. Flexor tendon grafts, 3-4-5th fingers.



Fig. 6: J. M. P., age 32. Tendon grafts, 2-3-4th fingers with pulleys 2nd-3rd fingers.

Summary

An attempt has been made to summarize the general and primary basic principles to

be considered in restoring the disrupted flexor tendon mechanism of the hand. An injured tendon will never function satisfactorily through an infected area or scar. Adequate first-treatment, knowledge of the fundamentals of physiology and anatomy of the hand, and adequate operating room facilities are essential for good hand surgery. Personal experience, including the results in 57 cases with 94 tendon grafts is presented.

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DISCURSO

AMOR Y SERVICIO AL PUEBLO

Luis A. Izquierdo Mora, MD

Esta noche es noche memorable para mí, ya que la considero una despedida, por cuanto será la última vez que me dirija a ustedes oficialmente en mi carácter de Presidente de nuestra Asociación. Créanme ustedes que me he desvelado muchas noches pensando en todas las cosas que en tan breve tiempo tendría que decirles, pero trataré, a grandes rasgos, de llevarles mis puntos de vista.

Para lograr este fin, he decidido plagiar a uno de los hombres por quien siento un gran respeto y admiración en Puerto Rico, que lo es nuestro Excelentísimo y Reverendísimo Arzobispo Monseñor Luis Aponte Martínez, quien en ocasión de la celebración del Día del Médico, abundó en el interesante tema "Amor y Servicio al Pueblo".

Antes de proseguir en el desarrollo de este tema, quiero aprovechar para dar las gracias más sinceras a todos mis compañeros que tuvieron a bien elegirme para este honroso y digno puesto de Presidente, y no puedo proseguir sin hacer llegar a ustedes mis impresiones de la gran experiencia, del regocijo y del gran honor y satisfacción que me ha proporcionado el haber tratado de cumplir con mi deber.

Pronunciado durante la Sesión Inaugural de la Sexagésimoquinta Asamblea Anual de la Asociación Médica de Puerto Rico, celebrada en el Hotel San Juan Intercontinental del 14 al 18 de noviembre de 1967.

¿Por qué debemos los médicos pensar que por el hecho de ser médicos debemos permanecer aislados en los cuatro murallones de nuestras oficinas?

No, mis queridos compañeros y amigos. El médico es muchísimo más; el médico tiene que estar presto a curar un enfermo, a salvar una vida; pero también tiene que estar en disposición de darse para todo aquello que signifique el bienestar de la ciudadanía.

Desde mis tiempos de estudiante he venido leyendo artículos que hacen mención de aquella famosa tertulia que se celebraba en la farmacia de nuestros antepasados, en la cual el médico, el farmacéutico, el alcalde y el cura se sentaban frente a la botica del pueblo a dirimir los asuntos importantes, tanto en el campo de la salud, como en el campo político, cívico, religioso y cultural. En aquella época, la imagen del médico estaba muy por encima de lo que está actualmente. Pensemos en el progreso habido en nuestra Isla, progreso económico, progreso científico; pensemos en todas las facilidades que se le ofrecen al médico para poder brindar los mejores servicios de salud; pensemos en los adelantos de la ciencia médica, gracias a los cuales se ha prolongado la vida, con una consiguiente reducción en la mortalidad y morbilidad.

Si pensamos en todos estos factores, es justo que nos preguntemos por qué ha disminuido nuestra imagen individual y colectiva.

La experiencia vivida por este servidor durante esta última década nos demuestra a saciedad que esto se debe principalmente a cinco factores:

1) A los cambios sociales y económicos ocurridos en estas últimas tres décadas;
2) A la apatía e indiferencia de compañeros médicos, los cuales todavía creen que la misión del médico es única y exclusivamente atender diligentemente a sus pacientes;
3) A los proyectos propulsados por los planificadores de los servicios de salud, los cuales en muchas ocasiones están encaminados hacia el tratamiento en masa, destruyendo la personalidad individual tanto del paciente como del médico;
4) Una merma en los valores morales y espirituales; y
5) A la desaparición gradual del médico de familia.

Amor y servicio; dos palabras tan cortas que encierran un significado tan grande. He aquí la fórmula; he aquí la llave que abrirá las puertas que habrán de restaurar la imagen del médico en Puerto Rico.

¿Cómo habrá de hacerlo? Es necesario que el médico vuelva a luchar hasta conseguir el liderato perdido, no tan sólo en el campo de la salud sino también en todos los aspectos que tiendan al bienestar de nuestro pueblo.

Este constituye nuestro gran reto, y podría decirles que estoy plenamente convencido de que el futuro de nuestra profesión depende de lo que todos y cada uno de nosotros hagamos por nuestro país.

Veamos lo que a nuestro entender constituye la base de esta restauración:

Primero: El médico tiene que ser el mejor amigo del paciente. Podríamos decir que esta es la piedra angular de las relaciones entre uno y otro, basándose esta amistad en una base de fe, respeto y confianza. Esa amistad es la que abre la mente y el corazón del paciente por medio de la cual se conocen aquellas interioridades necesarias para hacer un buen diagnóstico y un buen tratamiento.

Es obvio que para lograr este ambiente el paciente debe estar en libertad de poder escoger su médico de fe y confianza.

Segundo: El médico tiene que actuar como consejero. En la intimidad del consultorio, en el diálogo con el paciente, un buen consejo dado a tiempo puede salvar mejor una vida que la medicina recetada.

Conviene señalar el hecho de que el médico tiene la obligación de aconsejar cívicamente a sus pacientes sobre todos los problemas de nuetra comunidad.

Tercero: El médico tiene que continuar actuando como confidente. El médico es la única persona en quien el paciente confía sus debilidades y problemas. Como el sacerdote en el confesionario, así oye el médico las cuitas de sus pacientes, y no solamente utilizando ese conocimiento para ayudarle a curar su cuerpo, sino también para llevarle a su alma un mensaje de paz y de tranquilidad espiritual. Por eso no nos debe extrañar que la atención médica esté considerada por todos como un servicio muy especial y personal.

Cuarto: El médico tiene que actuar como científico. Para ser médico se requiere uno de los programas educacionales más largos y rigurosos, lo que es más, el estudio no termina cuando finalmente se obtiene el diploma y la licencia. Para mantenerse medianamente informado acerca de los nuevos descubrimientos en el campo de la medicina, él debe seguir estudiando mientras ejerza su profesión, recetándole al paciente, como ha dicho el distinguido galeno puertorriqueño,

Dr. Ramón M. Suárez, "recetándole al paciente del 1967 los descubrimientos y drogas maravillosas de 1967 y no del año 1930".

Quinto: *El médico tiene que ser un educador.* Existe la imperiosa necesidad de instruir al paciente en el buen uso de las medicinas, en la formación de buenos hábitos, costumbres, normas de higiene y de vida, y en esta época moderna, sobre el buen uso de los servicios médicos, hospitalarios y de los seguros voluntarios prepagados de salud.

Sexto: *El médico tiene que ser planificador.* Tenemos que asumir el liderato en la búsqueda de soluciones a nuestros problemas de salud. Soluciones justas, las cuales sean factibles, flexibles, constructivas, positivas y sobre todo soluciones puertorriqueñas, planificando tanto a corto como a largo plazo, con tal de que cuando venga el año 2000 podamos decir con entera satisfacción, "hemos honrado el compromiso que se supone vivir en nuestra época".

Séptimo: El médico debe observar una conducta moral intachable. Partiendo de la premisa de que el médico no tiene lo que se llama vida privada, debe servir de ejemplo a su comunidad como buen ciudadano, como buen hijo, como buen esposo y como buen padre, cumpliendo a cabalidad con los mandamientos de la ley de Dios y los cánones de ética profesional.

Además del médico tener una gran responsabilidad ante su paciente como individuo, tiene otra gran responsabilidad ante la comunidad como conglomerado social. El médico tiene que interesarse y participar activamente en todo lo que pueda ser de beneficio a la sociedad en que convive y adentrarse en las actividades cívicas, religiosas, culturales y políticas, entre otras.

El médico tiene que tomar participación en todas aquellas actividades cívicas de su pueblo que así lo ameriten, no solamente como ciudadano sino que también debe ofrecer toda su cooperación de índole profesional.

El médico debe participar activamente en la religión de su convicción, pero además debe colaborar en todas aquellas actividades que en beneficio de la comunidad organizan las diferentes iglesias, sin distinción de credo o denominación.

El médico debe tomar participación activa en la vida cultural de su pueblo. Se supone que sea él una de las personas más preparadas desde el punto de vista educativo, así pues, tiene un sitio ineludible en el campo de las artes y las letras. Todos tenemos la indeclinable responsabilidad de hacer nuestras aportaciones a la cultura de nuestro país.

El médico debe participar activamente dentro del partido de su predilección, en la política de su pueblo para poder servir a sus conciudadanos, a sus pacientes, en la forma más liberal y democrática, sobre todo, ayudándoles a conseguir y a preservar todos aquellos derechos que poseen en la patria en que vivimos.

He señalado lo que a mi manera de entender constituyen los factores principales que obstaculizan una mejor imagen del médico puertorriqueño. Toca a nosotros ahora el observar las mejores reglas de buena conducta hacia el ciudadano, hacia el paciente, hacia la comunidad en que vivimos, a los fines de llegar a la feliz realización de nuestras metas e ideales, que no son otros qué los de proveer a todos los ciudadanos por igual la más alta calidad de servicios médicos.

Les aseguro a ustedes en esta noche, que con *amor y servicio al pueblo* no tan sólo levantaremos la imagen del médico si que también restauraremos el liderato médico

en todas las actividades cívico-sociales antes mencionadas.

Estamos entrenados para combatir las enfermedades y los problemas de salud. Aunque no estudiamos para combatir legislación que afecte adversamente la salud de nuestros pacientes, no claudicaremos. No habrá descanso mientras existan esos problemas. Estamos preparados para hacer frente a cuantos escollos encontremos en nuestro camino. *Nuestra intención y la verdad de nuestros postulados nos amparan.*

Los días pasan velozmente y las horas en el reloj de arena van marcando el camino que hemos recorrido en nuestra efímera existencia. Un año ha transcurrido ya desde que ustedes me hicieron el honor de elegirme presidente. Hoy ha llegado el momento de la despedida. Nada me ha proporcionado tanta felicidad como el haber podido servir a mi Asociación, a mis compañeros, a mi profesión y a mi pueblo. Nunca olvidaré esta gran oportunidad, y créanme que los llevaré muy hondo en mi corazón.

Cuatro cosas deseo aconsejarles, que a mi juicio lo abarcan todo:

Primero: Poner toda nuestra fe en Dios, quien es guía y luz de la humanidad entera.

Segundo: Buscar la más estrecha unión entre todos, recordando aquellas palabras de Cristo, "Amaos los unos a los otros".

Tercero: Defender con todas nuestras fuerzas la pureza de nuestra profesión.

Cuarto: Continuar nuestra lucha con más ahinco en la búsqueda de soluciones justas para los problemas de salud de nuestro país.

Y ahora para terminar, deseo ofrecerme a las órdenes del nuevo Presidente, de la nueva Junta de Directores y de todos ustedes, que en todo momento me brindaron atenciones y cortesías que este humilde servidor no merece.

Dios permita que los días por venir sean días de éxito, de progreso y de enaltecimiento para nuestra profesión; y que brille el sol a lo largo del camino que habremos de recorrer en pos de una mejor calidad de servicios, a través de libre selección del médico de fe y confianza, para todos los pacientes por igual, irrespectivo de su condición social, económica, de su raza, creencias religiosas y políticas, en beneficio de la salud, el bienestar y la prosperidad de este pueblo de Puerto Rico que tanto queremos todos.

INFORME ANUAL DEL PRESIDENTE DE LA ASOCIACION MEDICA DE PUERTO RICO

Luis A. Izquierdo Mora, MD

Sr. Presidente de la Cámara de Delegados. Sres. Miembros de la Junta de Directores. Sres. Presidentes de las Sociedades de Distrito, amigos todos:

Constituye para mí un verdadero privilegio y un gran honor el poder dirigirme a ustedes en la celebración de la tercera y última reunión de la Cámara de Delegados de este año. Primero que nada deseo extenderle a todos los miembros de la Junta de Directores, a los miembros de la Cámara de Delegados y a todos los miembros de la AMPR, a todos los médicos de Puerto Rico y al personal administrativo de nuestra Asociación, las más expresivas gracias por su valiosa ayuda en este año de gestión presidencial. Sin vuestro más decidido apoyo y colaboración nuestras gestiones hubieran sido estériles e infecundas.

Trataré de hacer un breve resumen de algunas de las actividades más sobresalientes realizadas durante este año, gracias a la labor conjunta y al unísono de todos y cada uno de ustedes:

Abortos criminales: Nuestra oferta de recompensa a la persona cuya evidencia conlleve a la convicción de un médico, enfermera o particular ha estado en pie durante todo el año. Repudiamos con todas nuestras fuerzas a esos señores que dicen llamarse médicos y que se dedican a esta práctica criminal.

Abortos terapéuticos: Se encuentra bajo estudio de la Sección de Obstetricia y Ginecología y del Comité de Medicina y Religión el problema de la paternidad responsable.

Administración: La labor realizada por todo el personal administrativo de nuestra Asociación ha sido excelente y en muchísimas ocasiones más allá en el cumplimiento del deber.

Agape a legisladores: Se llevó a cabo un ágape en honor a los legisladores de nuestra Isla, el cual resultó, en todos sus aspectos, un éxito rotundo.

Agrupaciones cívicas: Hemos tenido la oportunidad de colaborar estrechamente con todás las agrupaciones cívicas del país, a través de la celebración conjunta de clínicas gratuitas. Nos han brindado la oportunidad de dirigirle la palabra a más de 100 clubs cívicos, donde hemos podido llevar la posición de nuestra Asociación sobre diversos temas de salud.

Agrupaciones paramédicas: Hemos tenido la oportunidad de reunirnos con todas las agrupaciones paramédicas del país y dialogar extensamente sobre los problemas de salud de nuestra Isla, aprovechando la oportunidad para presentarles soluciones a los problemas de salud.

Anuncio lumínico: Este ha sido de gran utilidad en nuestro empeño de servirle a la comunidad. Ha sido sumamente solicitado

por todas las agrupaciones que bregan con los problemas de salud.

Asociación de Alcaldes: Las relaciones de nuestra Asociación con la Asociación de Alcaldes de Puerto Rico, presidida por el Honorable Adrián Torres y dirigida por su Secretario Ejecutivo, el Honorable Leandro Cabranes, han sido en todo momento extremadamente cordiales y sumamente fructíferas, reinando un ambiente de paz y con fraternidad, culminando con el nombramiento de nuestro querido Expresidente, el Dr. Egidio S. Colón Rivera, como Asesor Médico en su Junta de Directires.

Asociación de Médicos Gubernamentales: Nuestras relaciones con la Asociación de Médicos Gubernamentales a través de su Presidente, el Dr. James Suárez, y de su Secretario Ejecutivo, el doctor Miranda, han sido sumamente beneficiosas. Nos hemos brindado la más decidida cooperación y recibimos su apoyo en nuestra campaña Operación Igualdad. Hemos participado de sus reuniones discutiendo ampliamente entre otros: 1) la creación de cursos Post-Graduados para médicos que no han aprobado su reválida y que ejercen la profesión con licencias especiales; a través de aportaciones legislativas para la creación de los mismos; 2) la creación de cuotas escalonadas en nuestra Asociación, para médicos que trabajen a tarea completa con el gobierno; 3) una justa retribución a base de pagos por paciente visto; 4) seguros que los cobijan; 5) sus relaciones con el Departamento de Salud, Asociación de Alcaldes y Tribunal Examinador de Médicos.

Asociación Médica Americana: Nuestro delegado, el Dr. Carlos Bertrán, y nuestro Delegado Alterno, el Dr. Carlos Berrocal, nos representaron en la Convención Semianual celebrada en Las Vegas, Nevada, llevando ante el seno de ésta una resolución sobre la inclusión de la libre selección de médico y hospital para los pacientes indigentes bajo el Título XIX, la cual fue aprobada por unanimidad. Representamos a nuestra Asociación en la Convención Anual celebrada en Atlantic City, New Jersey, donde tuvimos la oportunidad, además de participar activamente en dicha Convención, de ofrecer acogida a miles de participantes de dicha Convención en un "Hospitality Suite" que montamos, gracias a los esfuerzos de los doctores Ovidio Rodríguez, José Alvarez de Choudens, Carlos Bertrán, Carlos Berrocal, César Rosa Febles, Luis F. Sala, Carlos García Montes de Oca, Eladio Montalvo Durand, Lydia G. de Montalvo, y muy en particular, del Sr. Daniel Rigau. Nuestras esposas e hijos colaboraron grandemente formando un combo musical para mayor lucidez de este evento. Debemos cada día participar más activamente en dichas convenciones, ya que a través de ellas se pone muy en alto el nombre de la AMPR, y reclutar más miembros para dicha Asociación. Las gestiones realizadas por el personal de la oficina central en Chicago, y muy en particular por el personal de la oficina de Washington, encabezados por el Dr. Royg Lester, respecto a las enmiendas al Seguro Social de 1967, han sido de un valor incalculable para el pueblo de Puerto Rico y de nuestra Asociación.

Asociación Médica Mundial: Estuvimos representados en la celebración de la reunión de la Asociación Médica Mundial por el doctor José Gallardo, el cual oportunamente nos remitirá un informe.

Asociaciones Voluntarias: Hemos trabajado hombro con hombro con casi todas

las asociaciones voluntarias de nuestro país, y hemos recibido su más decidida cooperación, brindándole a su vez nosotros asesoramiento cuando así se nos ha pedido.

Auxilio Médico Mutuo: La labor realizada por la Junta del Auxilio Médico Mutuo, presidida por el Dr. Víctor Rivera, merece nuestra felicitación más sincera, al igual que el Comité encargado de hacer estudios sobre diferentes seguros para nuestros socios, que tan hábilmente ha sido presidida por el distinguido miembro de esta Asociación, el doctor Manuel Pavía Fernández. Opinamos que se debe poner en vigor, tan pronto así se apruebe, el Reglamento preparado por dicha Junta y más aún, creemos firmemente que esta fuente de ayuda y Monte Pío para las viudas y beneficiarios bajo ninguna circunstancia debe desaparecer. En esta forma y para propósito de nuestra historia, hago clara de una vez y para siempre mi posición personal entendiendo que me hago eco de numerosas esposas de compañeros médicos, las cuales en estos mismos términos así lo han manifestado.

Boletín Informativo: Se publicaron solamente nueve ediciones de éste, siguiendo vuestro mandato, y tratando de llevar en cada cual información y orientación a todos los médicos de Puerto Rico, así como a las autoridades legislativas, estatales y municipales. La labor realizada por el Sr. Gregorio Díaz en la confección de éste ha sido digna de encomio. Opinamos que el costo de este Boletín debe sufragarse por sí solo consiguiendo entidades que lo patrocinen.

Boletín Médico: Este se puso al día habiendo sacado durante este año 17 ediciones, mejorándose a la vez su formato y su calidad. Para el próximo enero el Boletín sufragará sus propios gastos, esperando que eventualmente deje beneficios a nuestra Asociación y que se publiquen en él más artículos científicos y de otra naturaleza. La labor realizada por el doctor Julio V. Rivera, su Junta, sus asesores, por los señores Daniel Rigau y Eulogio Bermúdez es digna de encomio.

Casa del Médico: Participamos en el acto inaugural de la Casa del Médico de Ponce. El Comité organizador, que tan hábilmente dirige el doctor Carlos Quilichini, ha realizado una obra imponente, la cual debe servir de ejemplo a todas las sociedades médicas de distrito.

Circulares: Se han enviado durante este año alrededor de 50 circulares a la matrícula donde se ha tratado de llevar información sobre el desarrollo de programas de nuestra Asociación.

Comité Asesor Título XIX: Tuvimos la oportunidad de presentar nuestra posición en cuanto a una mejor implementación del Título XIX en nuestra isla la cual resulte en una mejor calidad de servicios para los pacientes médicamente indigentes de nuestra isla, y que el presente plan, según ha manifestado el Departamento de Salud, Educación y Bienestar federal, presenta 16 deficiencias capitales, luego de haber inspeccionado dicho plan diez autoridades. Esperamos y confiamos se le haga justicia social médica a todos los pobres de P.R.

Comité Pro-Fondos AMPR: Bajo la presidencia del Dr. Rafael Cuevas Zamora y con la más decidida colaboración del Sr. Raúl Gándara, de númerosos médicos y ciudadanos, se llevó a cabo un banquete para recaudar fondos para nuestra Asociación. Dicha actividad resultó en un éxito rotundo.

Comité de Enfermedades del Corazón, Cáncer y Apoplejía: El doctor Ramón M. Suárez, Presidente de este importante Comité, nos representó en Washington en la primera reunión celebrada a nivel nacional para la implementación de programas regionales. La labor de los doctores Luis F. Sala y Luis Guzmán López en este Comité ha sido extremadamente útil. El doctor José Alvarez de Choudens y un servidor hemos participado en las reuniones de dicho Comité.

Comité de Etica: El doctor Walter J. Benavent y los miembros de este Comité en forma rápida y extremadamente acertada han resuelto numerosos casos en los cuales la ética ha estado envuelta. Reciban los miembros de este Comité un espaldarazo por sus rápidas actuaciones en los casos sometidos a su consideración, ya que han tomado acción también en casos de médicos no miembros de la AMPR.

Comité de Historia y Cultura: El ilustre hombre de letras y compañero médico, doctor Salvador Arana Soto, ha realizado una fecunda tarea en el cumplimiento de sus deberes, al igual que todos los miembros del Comité, participando activamente en la égida al Dr. Diego Alvarez Chanca conjuntamente con la Sociedad de Médicos Graduados de Universidades Españolas. Bajo el auspicio de la Asociación, el doctor Arana Soto ha escrito varios libros de valor incalculable. Este Comité tomó parte activa en la celebración del Día del Médico y en numerosos actos culturales celebrados en nuestra isla. Tenemos que intensificar cada día más nuestra participación en este importante aspecto y tratar por todos los medios a nuestro alcance, en un futuro cercano, de poner al día el libro de la Historia de la Medicina en Puerto Rico y crear oficialmente el Museo Médico.

Comité de Medicina y Religión: La dinámica actuación del presidente de este Comité, el doctor Osvaldo Lastra Morales, de sus miembros y de su coordinador, el señor Gregorio Díaz, ha sido fundamental hacia el esfuerzo mancomunado en la integración de la medicina y la religión en beneficio del paciente. Han brindado numerosos paneles, conferencias, foros, y preparado, de su propio presupuesto, numerosos materiales impresos. La desinteresada colaboración del Rev. Antonio Rivera Rodríguez y de los RR.PP. Jaime Capó y Agustín fue de vital importancia en el desarrollo de las actividades celebradas.

Comité de Finanzas: La labor del Comité de Finanzas, presidido por el querido compañero doctor Héctor A. Bladuell, ha sido extraordinaria. Opinamos que para que nuestra Asociación pueda llevar a cabo sus programas en beneficio de nuestro pueblo debe de operar con un presupuesto no menor de $225,000.00. Bajo ningún concepto se puede operar nuestra Asociación con un presupuesto no realista, ya que esto ataría y amordazaría la brillante labor que se propone realizar nuestro Presidente Electo el doctor José A. Alvarez de Choudens.

Comité de Resoluciones: La dinámica labor realizada por el Presidente de este Comité, el doctor Fernando Cabrera, y sus miembros, ha sido básica para nuestra Asociación estudiando y opinando sobre numerosas resoluciones.

Comunicados de Prensa, Radio y Televisión: Se han enviado durante el transcurso de este año más de 350 comunicados de prensa, radio y televisión, en los cuales hemos tratado de llevar un mensaje a nuestro pue-

blo sobre las actividades que hemos venido desarrollando en su beneficio. Hemos recibido la más decidida colaboración de la prensa, radio y televisión y pido a esta Hon. Cámara la aprobación por unanimidad, de la resolución de agradecimiento a estas instituciones.

Consejo Científico: El doctor Amaury Capella y su Consejo han desplegado una labor titánica durante todo el año a través de sus Comités, particularmente a través de los de Programación Científica, Actividades Sociales, Estudios Post-Graduados, Audio Visual, Biblioteca, etc. Vayan a estos distinguidos médicos nuestra más cordial enhorabuena por el éxito alcanzado en la consecución de sus metas.

Consejo Judicial y Administrativo: El doctor Lino Feliciano y su Consejo han tenido un año extremadamente atareado, cumpliendo a cabalidad con todo lo que se les ha encargado y generando nuevas ideas. A través de su Comité de Mediación y Querella, Constitución y Reglamento, Anuncios, Credenciales, etc. han realizado toda esta labor. Han estudiado numerosos seguros suplementarios y están en planes de desarrollar una cooperativa de crédito para nuestros socios, además de haber estudiado a cabalidad el asunto de los nombres de los médicos en las páginas amarillas de la guía telefónica.

Consejo de Relaciones Públicas: La labor del Presidente del Consejo de Relaciones Públicas, el querido amigo doctor Marino Blasini, y sus miembros del Consejo, ha sido de vital importancia para nuestra Asociación en la preparación de numerosos actos, foros, ágapes, seminarios, conferencias. Celebraron cursos de adiestramiento para los miembros del Foro de Oradores; auspiciaron el Dispensario conocido como la Playita, en Santurce, cursos de resucitación para bomberos y policías, etc.

Consejo de Política Pública: Constituye este Consejo nuestro benjamín y gracias a la eficiente labor del doctor José A. Pereyó y los compañeros de este, se ha realizado una gran labor. Han trabajado en numerosos proyectos que fueron presentados en nuestra Legislatura, sistemas de amigos, orientando a estos últimos en la formación de nuevos conceptos sobre la práctica de la medicina. El potencial de este Consejo es incalculable.

Consejo de Servicios Médicos: Bajo la hábil presidencia del doctor Rafael Cuevas Zamora y los miembros de su Consejo, se llevaron a cabo innumerables estudios sobre los serios y graves problemas en la prestación de servicios médicos. Se revisó y se puso al día nuestro plan Operación Igualdad, el cual recibió el apoyo de casi todas las agrupaciones paramédicas del país. Se estudiaron los casos del Hospital Presbiteriano, Auxilio Mutuo y San Carlos (conviene señalar el hecho que éste Hospital terminó sus relaciones con los planes de Uniones). Se revisaron numerosos planes de seguros; estudiaron a cabalidad las implicaciones de las enmiendas a la Ley de Seguro Social de 1967 y sometieron sus recomendaciones al efecto.

Consejo de Salud Pública: El Consejo de Salud Pública de nuestra Asociación, bajo la extraordinaria dirección del doctor Eladio A. Montalvo Durand y sus miembros ha realizado una tarea sumamente meritoria, entre las cuales señalamos: panel contaminación atmosférica, panel contaminación de agua, vistas públicas para la creación de un Departamento de Salud y un Departamento de Bienestar Público; tarjeta de identificación médica de emergencia; inspección sobre el terreno de problemas de saneamiento am-

biental en los pueblos de Trujillo Alto, Cataño, Toa Alta, Caguas, Santurce, etc.; investigación de numerosas querellas sobre problemas de saneamiento elevadas por ciudadanos; representación ante el Departamento de Salud y Legislatura sobre proyectos de ley, y reglamentos sanitarios en cuanto a restaurantes, cuarentena de ganado vacuno, aguas costaneras, etc; y numerosas actividades que aparecen en el informe de este Consejo.

Consejo de Educación Médica: Es fundamental, para la buena marcha de nuestra Asociación, la aprobación de un consejo de Educación Médica, máxime cuando el Consejo Científico de nuestra Asociación así lo estima pertinente.

Convención Semianual: Por primera vez en los tiempos modernos de nuestra Asociación, se llevó a cabo, con gran éxito, la Convención Semianual en la hospitalaria ciudad de Ponce. Creemos que esta actividad debe continuarse llevando a cabo, con la esperanza de que eventualmente se pueda celebrar en Arecibo y en Mayaguez. La labor realizada por el Dr. Gilberto Rodríguez y los compañeros médicos del Distrito Sur merecen nuestra más sincera felicitación.

Cuerpo de Capitanes Médicos en el Servicio de Bomberos: Hemos colaborado estrechamente con el señor Raúl Gándara, ofreciéndole nuestra más decidida colaboración a través de cursos de resucitación y otras materias. En todo momento hemos estado disponibles para cualquier caso de emergencia.

Cruz Azul de Puerto Rico: Hemos estado recibiendo durante este año la más decidida cooperación de la Cruz Azul en todo lo que le hemos solicitado. Nuestro más profundo agradecimiento a la Junta de Directores, la cual es presidida por el señor Agustín Vera Palma, y muy en particular a su Director Ejecutivo, el señor Arturo de la Cruz.

Departamento de Bienestar Social: Es de vital importancia para nuestro pueblo, la creación de un Departamento de Bienestar Social a la mayor brevedad posible en beneficio de nuestro pueblo, y así se lo hicimos saber a los presentes en la Convención del Colegio de Trabajadores Sociales, los cuales nos han brindado durante este año su más decidida colaboración, a través de su Presidente el señor Antonio Rodríguez.

Departamento de Salud: Hemos celebrado durante el año reuniones periódicas, en primer término, con nuestro querido exsecretario de Salud, doctor Mario Rubén García Palmieri, distinguido miembro de esta Asociación, durante su incumbencia, y con el nuevo Secretario de Salud, el doctor Manuel A. Torres Aguiar, hermano de esos grandes colaboradores de la Asociación, los doctores Luis y Carlos Torres Aguiar. En todo momento hemos mantenido relaciones sumamente cordiales, discutiendo las llamadas áreas blancas, grises y negras, llevando en cada mensaje la posición de la Asociación en cuanto a la solución a los problemas de salud de nuestra isla.

Departamento de Salud Mental: Apoyamos la posición de la Sección de Psiquiatría, Neurología y Neurocirugía de nuestra Asociación sobre la necesidad de la creación de un Departamento de Salud Mental en nuestra isla.

Dia del Médico: Se celebró el tradicional Día del Médico como en años anteriores. Creemos firmemente que las celebraciones llevadas a cabo durante este día deben de ser minuciosamente reevaluadas.

Diálogo con los Médicos: Hemos tenido

el privilegio de dialogar extensamente con más de 2,000 médicos de nuestra isla sobre los diferentes problemas de salud. Muchos de los proyectos que se han llevado a cabo han surgido de este diálogo continuo. El diálogo y la acción positiva nos llevará a un mejor entendimiento entre los médicos en beneficio de nuestros pacientes.

División Vertical entre los Planes Azules de Puerto Rico: Hemos estado presidiendo el comité de enlace de ambos planes azules. Esperamos que estas reuniones nos lleven a una feliz realización en cuanto a una división vertical entre ambos planes. El progreso de dicho acercamiento ha sido notorio y esperamos que su esfuerzo culmine muy próximamente.

Doctor Reinaldo Ferrer: Hemos recibido de este distinguido miembro de nuestra Asociación valiosísimo y desinteresado asesoramiento en cuanto a todos los proyectos federales que afectan al pueblo de Puerto Rico. Los médicos de Puerto Rico estamos en deuda de gratitud con el doctor Ferrer por sus actuaciones.

ECFMG: Gracias al esfuerzo mancomunado de todas las instituciones que laboran en los problemas de salud de nuestro país, se consiguió la eliminación del examen del ECFMG como requisito para poder ingresar a un internado reconocido. La implementación del alcance de esto está en manos, al presente momento, del Tribunal Examinador de Médicos, el cual muy probablemente lo implemente para marzo de 1968. Los médicos puertorriqueños ciudadanos americanos ya no tendrán que coger dicho examen, ya que entendíamos y entendemos que este estaba diseñado para estudiantes extranjeros.

Edificio: Se han llevado a cabo las reparaciones necesarias. Se instaló un nuevo cuadro telefónico, gracias al Distrito Este, y se han reorganizado nuestras oficinas. Nuestra Asociación ha estado abierta durante casi todos los días y noches del año, habiéndose celebrado más de 1,500 reuniones.

Escuela de Medicina: Hemos trabajado estrechamente con los doctores Adán Nigaglioni, Rector de Ciencias Médicas, y José Sifontes, Decano de la Escuela de Medicina, durante todo el año discutiendo ampliamente, entre otras cosas: 1) La creación de un curso post-graduado para los médicos que no han podido aprobar su reválida y que ejercen la profesión con licencias especiales; 2) la creación de una escuela médica post-graduada; 3) la creación de un Departamento de Medicina de familia y un programa de tutores médicos; 4) problema de la escasez de personal paramédico; 5) programa regional de enfermedades del corazón, cáncer y apoplejía; 6) la expansión de la Escuela de Medicina; 7) cursos de orientación a los estudiantes de medicina en cuanto a los problemas sociales, económicos y de salud del país. Comparecimos en vistas públicas ante el Consejo de Educación Superior, donde expresamos la posición de nuestra Asociación. Concurrimos como invitados de honor a los ejercicios de graduación del Recinto de Ciencias Médicas de la Escuela de Medicina de la UPR.

Fundación Médica de P. R.: Hemos colaborado activamente con la Fundación Médica de Puerto Rico, la cual fue fundada por nuestro querido ex-presidente, doctor José S. Licha, y la cual recientemente exaltó a su Presidencia al doctor Egidio S. Colón Rivera. Merece la Fundación Médica el más decidido apoyo de los miembros de la profesión médica del país y de toda la comunidad.

Junta Asesora de Hospitales: Tuvimos la

oportunidad de presentar nuestra posición sobre el problema de la construcción de facilidades médicas en Puerto Rico y la asignación de fondos federales de acuerdo con la letra y el espíritu de la ley. Nos place informar que en este año se han hecho asignaciones para la construcción de hospitales de la comunidad.

Naciones Unidas: A petición del Departamento de Estado de Puerto Rico, participamos activamente en la celebración de la "Semana de las Naciones Unidas". Esta actividad resultó en un éxito rotundo.

Nuestros Asesores: La labor realizada por el licenciado Salvador Casellas, el señor José Rivera Escalona, y Haskins & Sells, ha contribuído notablemente a la buena marcha de nuestra Asociación. Pido se apruebe por unanimidad una resolución de agradecimiento por su meritoria labor por sus asesoramientos respectivos.

Nuevos Distritos y Zonas: Opinamos que se debe reestudiar la creación de nuevos distritos y zonas dentro de nuestra Asociación.

Nuevos Socios: Se han logrado ingresar a nuestra Asociación durante este año 184 nuevos socios, a través de contactos y cartas personales a los no socios. Urge poner al día el manual de médicos de Puerto Rico para así poder llevar a cabo una labor más efectiva. Opinamos que las sociedades de distrito son de vital importancia para recolectar nuevos miembros y que se deben llevar a cabo actividades sociales de orientación y bienvenida a los compañeros médicos que ingresen en nuestras filas.

Operación Colombia, Venezuela y Santo Domingo: Se logró enviar a dichos países, gracias a la generosidad de la industria farmacéutica (Pro Salud) de nuestro pueblo y la de los médicos, medicinas y ropa en los momentos que habían sufrido los embates de huracanes o terremotos.

Operación Vitrinas: Bajo los auspicios de la Sección de Medicina General, la Academia de Medicina General, y de los doctores Lino Feliciano, Rafael Guerrero y Rafael Cuevas Zamora, se han alquilado numerosas vitrinas en los salones de nuestra Asociación, las cuales le han servido como medio de promoción a las casas farmacéuticas. Esta actividad se debe ampliar, ya que refuerza grandemente los ingresos de nuestra Asociación.

Paternidad Responsable: Se encuentra bajo estudio de la Sección de Obstetricia y Ginecología y del Comité de Medicina y Religión el problema de la paternidad responsable.

Programas Mensuales: Se llevaron a cabo todos los programas mensuales que se planearon al principio de año sobre tuberculosis, adicción a drogas, enfermedades del corazón, tarjeta de identificación médica de emergencia, cáncer, seguros médicos, enfermedades de la vista, retardación mental, enfermedades venéreas, diabetes y alcoholismo. Todas estas actividades resultaron en un éxito rotundo, gracias a la más decidida colaboración de los directores estatales de campaña. Creemos que esta actividad se debe seguir llevando a cabo, perfeccionándose cada día más.

Proyecto de la Cámara 292: Expresamos la posición de la AMPR en cuanto a este Proyecto, sobre la posibilidad de la creación de un seguro médico hospitalario compulsorio para toda la población, el cual pretendía proveer una cubierta mínima. Por considerarlo en detrimento de la salud de nuestro pueblo, y con el respaldo de más de 600,000 ciudadanos nos opusimos a dicho Proyecto, y presentamos soluciones alternas

a través de seguros médicos, farmacéuticos, dentales y hospitalarios voluntarios prepagados.

Proyecto del Senado 632: Respaldamos este Proyecto de Ley, el cual más luego se convirtió en la Ley 81, para estudiar nuevas modalidades de financiamientos en cuanto al costo de los servicios de salud. Al presente se están estudiando las áreas a ser escogidas.

Proyecto HR-89749: Se discutió ampliamente con el Sr. John Diamond la implementación de éste proyecto federal en nuestra isla, el cual propone una asociación entre los servicios tanto públicos como privados que se le brindan a nuestros pacientes.

Reconocimientos a la AMPR: Nuestra Asociación ha sido honrada durante este año al habérsele entregado distintivos de reconocimientos por la Cruz Roja, Colegio de Farmacéuticos de P.R., la Federación de Mujeres de P. R., Comité de Adicción a Drogas, y Sociedad Pro Niños y Adultos Lisiados.

Secciones de Nuestra Asociación: La inmensa mayoría de las secciones de nuestra Asociación han estado sumamente activas desarrollando: 1) reuniones mensuales, 2) conferencias educativas para los médicos y para el pueblo; 3) elaborando sus programas de convenciones; 4) desarrollando programas y proyectos para la comunidad. Opinamos que se debe considerar además el dar voz y voto a los presidentes de las secciones en esta Cámara de Delegados. Aprovecho esta ocasión para dar las más expresivas gracias por la colaboración que nos han brindado en el cumplimiento del deber.

Seguros: La firma Quiñones, Lessere-Wertheim, Inc. nos está realizando un estudio para planes de incapacidad, muerte accidental y cubierta médica mayor.

Seguros de Servicios de Salud: Hemos recibido durante este año la más decidida cooperación de la Triple S en todo lo que hemos solicitado. Nuestro más profundo agradecimiento a la Junta de Directores, la cual es presidida por nuestro querido compañero, el Dr. Angel Luis Rodríguez Rosado, y muy en particular, al señor Pedro Ortiz Aponte y a todo el personal de la Triple S.

Semana de la Salud de la Comunidad: Por primera vez en la historia, nuestra Asociación auspició la Semana de la Salud de la Comunidad en nuestra isla, basando ésta en 3 puntos cardinales: prevención de enfermedades venéreas, reclutamiento de personal paradémico, y la Feria de la Salud. Los esfuerzos titánicos del doctor Ovidio Rodríguez y su Comité Timón, hicieron posible esta celebración. Opinamos que esta actividad se debe llevar a cabo anualmente.

Señor Carlos Rosa Guzmán: Don Carlos ha sido durante este año nuestro brazo derecho en el asesoramiento de todos y cada uno de los programas de relaciones públicas que hemos llevado a cabo durante el año, el cual creemos que ha permeado y llegado al último rincón de nuestra isla. Reciba Don Carlos en su lecho de enfermo nuestra más calurosa felicitación y oración por su pronto restablecimiento.

Servicio Médico de Emergencia: Este está operando en varios pueblos de la isla. Opinamos que la implementación de este sistema debe de ser reevaluada, ya que constituye una necesidad imperiosa para nuestro pueblo.

Servicio Médico Voluntario: El cuerpo de médicos de servicios médicos voluntarios de nuestra Asociación ha estado disponible para entrar en acción en cualquier caso de escasez aguda de servicios médicos en algún pueblo de nuestra isla.

SAMA: Hemos colaborado activamente con dicha agrupación y participado en sus actividades. Se le entregaron las tarjetas de miembros de nuestra Asociación en un acto auspiciado por la Sociedad Médica del Distrito Este. Constituye esta Sociedad la cantera más rica de miembros para nuestra Asociación. Tenemos que continuar dándole cada día más nuestro más decidido apoyo y cooperación.

Sociedad de Internos y Residentes de P. R.: Ha habido un acercamiento mutuo entre ambas agrupaciones y hemos respaldado ante las autoridades pertinentes que se emita una opinión sobre el status de dichos compañeros médicos (estudiantes vs. empleados), aumento de sueldo a tono con el incremento en los costos de vida, y darle la debida protección con los seguros que ellos han solicitado.

Sociedad Médica de Estudiantes de España y México: Hemos mantenido correspondencia activa con dichas agrupaciones de futuros médicos y en nuestro reciente viaje a España discutimos ampliamente con los estudiantes de la Universidad Central de Madrid. Tenemos que continuar colaborando y orientando a estos futuros compañeros a través de nuestra Asociación y a través de la Fundación Médica de Puerto Rico.

Sociedades Médicas de Distrito: Constituyen las sociedades médicas de distrito el brazo derecho de nuestra Asociación. La labor realizada por sus presidentes, doctores Ovidio Rodríguez, Distrito Este; César Rosa Febles, Distrito Norte; José Luis Iturrino, Distrito Occidental; y Gilberto Rodríguez, Distrito Sur, ha sido extraordinaria y merece la más calurosa felicitación de esta Cámara. Dado el caso de que sus presidentes presentarán sus informes, no entro en detalles de la eficiente y extraordinaria labor que han realizado en pro de nuestra comunidad.

Tarjeta de Identificación Médica de Emergencia: Se repartieron a todo lo largo y a todo lo ancho de nuestra isla un millón de tarjetas de identificación médica de emergencia, donadas muy gentilmente por la Industria Farmacéutica Americana de Puerto Rico (Pro Salud). La labor realizada por el doctor Eladio A. Montalvo Durand y su Consejo merece la más calurosa felicitación de todos y cada uno de nosotros.

Título XVIII: Hemos estado en conversaciones con la Oficina del Seguro Social de nuestra isla, a través del Sr. Howard A. Davidson, planificando para el próximo período de inscripción para las personas de 65 años o más. Esperamos que ésta comience oficialmente el primero de enero de 1968, tan pronto se sepa la nueva prima de dicho seguro.

Vicepresidentes de la A.M.P.R.: Es fundamental para la buena marcha de nuestra Asociación enmendar nuestra Constitución al efecto de que se creen a nivel de la Junta de Directores, tres plazas de vicepresidentes. Dichos Vicepresidentes llenarían un vacío existente al presente, brindándole al Presidente en funciones una gran ayuda.

Comisión Social del Gobernador: El doctor José Alvarez de Choudens y un servidor tuvimos la oportunidad de exponer la posición de la AMPR ante esta Comisión, compuesta por el Secretario del Trabajo, Hon. Alfredo Nazario, el Secretario de Salud, Hon. Manuel A. Torres Aguiar; el Director de la CRUV, señor Carlos Alvarado; el Director del Programa de Oportunidades Económicas, señor Rafael Torregrosa, la cual está estudiando los problemas

de salud del país. Testificaron esa noche también, el Honorable Secretario de Salud, doctor Manuel A. Torres Aguiar, y los ex-secretarios de Salud doctores Mario R. García Palmieri y Guillermo Arbona. En otra vista subsiguiente testificaron los doctores Adán Nigaglioni y José Nine Curt, entre otros.

Enmiendas a la Ley de Seguro Social (Proyecto HR-5710 y HR-12080): Les incluyo copia de nuestra ponencia ante el Comité de Finanzas del Senado de los E.U. del 18 de septiembre de 1967, copia de la carta que recibimos del Hon. Presidente de los E.U., Lyndon B. Johnson, y copia del editorial del periódico "El Imparcial" titulado "Operación Igualdad", del 10 de noviembre de 1967, las cuales se explican por sí solas. En nuestro último viaje a Washington, hace 10 días, tuvimos la oportunidad de entregarle a los altos funcionarios de dicho Comité las 200,000 firmas recogidas en Puerto Rico, lo que solidificó nuestra posición.

Nuestra más sincera felicitación a los honorables miembros de esta Cámara de Delegados, a la Junta de Directores, Consejos, Comités, Secciones, Academias, Alumnae, por su más decidida colaboración en este año.

Es éste el resumen a grandes rasgos de algunas de las actividades realizadas por los Distritos, Consejos, Comités, y nuestra Junta de Directores durante este año.

Los días pasan velozmente, y las horas en el reloj de arena van marcando el camino que hemos recorrido en nuestra efímera existencia. Un año ha transcurrido ya desde que ustedes me hicieron el honor de elegirme Presidente. Hoy ha llegado al momento de la despedida. Nada me ha proporcionado tanta felicidad como el haber podido servir a mi Asociación, a mi pueblo, a mis compañeros, y a mi profesión. Nunca olvidaré esta gran oportunidad; y créanme que los llevaré muy hondo en mi corazón.

Cuatro cosas deseo aconsejarles, que a mi juicio lo abarcan todo:

Primera: Poner toda nuestra fe en Dios, quien es guía y luz de la humanidad entera.

Segunda: Buscar la más estrecha unión entre todos, recordando aquellas palabras de Cristo, "Amaos los unos a los otros".

Tercera: Defender con todas nuestras fuerzas la pureza de nuestra profesión.

Cuarta: Continuar nuestra lucha con más ahinco en la búsqueda de soluciones justas para los problemas de salud de nuestro pueblo.

Y ahora, para terminar, deseo ofrecerme a las órdenes del nuevo Presidente, de la nueva Junta de Directores y de todos ustedes, que en todo momento me brindaron atenciones y cortesías que este humilde servidor no merece.

Dios permita que los días por venir sean días de éxito, de progreso y de enaltecimiento para nuestra profesión; y que brille el sol a lo largo del camino que habremos de recorrer en pos de una mejor calidad de servicios a través de libre selección del médico de fe y confianza para todos los pacientes por igual, irrespectivo de su condición social, económica, de su raza, creencias religiosas y políticas, en beneficio de la salud, el bienestar y la prosperidad de este pueblo de Puerto Rico que tanto queremos todos.

IN MEMORIAM

A. OLIVERAS GUERRA, MD

A. A. Cintrón Rivera, MD

Al pedirme el Dr. Freddie Borrás y Doña Ana Inés Armstrong Vda. de Oliveras que asumiera cargo de la apología en este acto, pensé de primera intención que había en Puerto Rico muchas otras personas que podían hacerlo mejor que yo, y que tuvieran el don de palabra necesario para un acto como este. Pero al mismo tiempo, la amistad que me unió a él y la admiración que siempre tuve por él, no me permitieron decir que no. Pensé además, que sería para mí verdadera satisfacción el poder decir estas humildes palabras.

El famoso novelista inglés, Robert Louis Stevenson, escribió muchos años atrás lo siguiente:

"Hay hombres y tipos de hombres que sobresalen sobre las muchedumbres; el soldado, el marinero, el artista, el político, y miembros del clero, pueden sobresalir con frecuencia; sin embargo, hay uno, el médico, quien por regla general se distingue. El es la flor de nuestra civilización y cuando la estadía del hombre en esta tierra llega a su fin, para solamente quedar en el pasado, se pensará de él, (el médico) como una persona que ha tenido poco de los defectos del período en que vivió, pero más notablemente, ha demostrado las virtudes de su raza. El médico tiene abundancia de *generosidad,* como es posible en aquellos que practican un arte; tiene *discreción,* probada por los cientos de secretos que sus pacientes le han confiado; tiene *tacto,* probado en miles de oportunidades, y lo que más importante quizás, tiene un *alma valiente, llena de ternura* y de *alegría.* Por esta razón, el médico lleva consigo al lecho del enfermo, cierto grado de alegría, de esperanza, y muchas veces, aunque no todas las veces que él quisiera, también trae la mejoría y la curación del enfermo."

Esta descripción del médico le cuadra perfectamente a la persona que fue el doctor Oliveras Guerra. Fue él una persona multifacética, y como tal, es relativamente fácil encontrar adjetivos para describir su vida y su obra. Como *hombre puertorriqueño,* el doctor Oliveras fue un ser generoso, lleno de dedicación, de nobleza y de dignidad. Su manera de ser, apacible, diplomática y tan ecuánime, le ayudaba a enfrentarse a las múltiples vicisitudes que surgen siempre en una vida personal y profesional tan activa como la de él. El doctor Oliveras Guerra fue esposo ejemplar, y padre único.

Vemos en su compañera, doña Ana Inés, y en su hijo, el hoy Dr. Enrique Oliveras Armstrong, la influencia de este gran hombre. Particularmente lo vemos en su hijo, en la manera de ser, la manera de hablar, la manera de pensar, en fin, en todo su ser, hay mucho del doctor Oliveras.

Para saber cómo era como abuelo, solamente aquellos de nosotros que tuvimos el

**Semblanza o apología del doctor Oliveras en ocasión de la inauguración del dispensario Dr. A. Oliveras Guerra, en Sabana Llana, Río Piedras, Puerto Rico, el día 18 de julio de 1967.*

privilegio de visitarle cuando estaba jugando con sus nietecitas nos dimos cuenta del gozo tan grande que significaba para él el estar junto a ellas. No sólo gozaba con tenerlas a su lado, sino que también aprovechaba toda ocasión para enseñarles muchas cosas con cariño. Desde este punto de vista, el Doctor no se ha ido, pues parte de él se encuentra en su hijo, y parte de él, se encuentra en sus nietecitas.

Como *médico* y *cirujano,* el Doctor representaba lo mejor de nuestra profesión. Tenía los atributos que el escritor Robert Louis Stevenson le atribuye a los médicos. Su dedicación al estudio, al mejoramiento profesional, al servicio al público, lo ponían de relieve dentro de su profesión. Las palabras del periodista Rafael Rivera Santiago, escribiendo en el periódico "El Día", de Ponce, refleja lo que era este distinguido cirujano en su profesión.

"La muerte del doctor Oliveras Guerra arrebata a nuestro pueblo un soldado del bien de la caridad cristiana en sus más altas y profundas manifestaciones. El era uno de ese tipo de médico rápidamente en desaparición de nuestro medio, que practicaba su profesión como un sacerdocio. No era un comerciante de la medicina, era un abnegado, un altruista, y dadivoso de su ciencia, cuya principal motivación no eran los honorarios que pudiera cobrar sino la íntima satisfacción de socorrer al enfermo y ver a éste de nuevo saludable. Era un cirujano notable y su notable humildad era signo de grandeza, grandeza de alma y grandeza de corazón, era crisolada y granítica su integridad profesional y ciudadana, y era suave su trato y jovial su carácter, propenso al chiste y a la anécdota."

Es interesante notar que la personalidad multifacética del doctor Oliveras Guerra lo condujo hacia campos fuera de su profesión. Desde bien temprana edad desarrolló un interés grande por las artes, particularmente *la pintura.* En sus últimos años de vida fue aprovechado discípulo de Guillermo Sureda. Hemos visto y apreciado en el Hospital Oncológico muchas de sus obras, y su familia conserva gran número de sus óleos y acuarelas. Además, fue un humanista, lector incansable y amante de la música y del teatro.

Al originarse un nuevo *partido político* en Puerto Rico, ya finalizando la década de los 30, el doctor Oliveras Guerra se abanderizó a este partido porque creía de todo corazón en la necesidad imperiosa de hacer algo por el pueblo puertorriqueño. Ayudó todo lo más posible, dentro de lo que su profesión le permitía, y por un tiempo tuvo la gran tentación de dedicar la mayor parte de sus esfuerzos a la política, pero no obstante, su profesión de médico y cirujano lo retuvo.

El doctor Oliveras Guerra nació en Arecibo el 4 de enero de 1898, y cursó sus estudios primarios en su ciudad natal. Completó la premédica en la Universidad de Puerto Rico en el 1920. Se recibió de doctor en medicina en la Universidad de George Washington en 1924 e hizo su internado en el Hospital Municipal de Santurce. Sirvió como médico titular en Jayuya por un tiempo y vino a la capital para convertirse en ayudante del doctor Díaz García en la Clínica que hoy día se conoce como Hospital Pavía. Desde aquel entonces, se dedicó a la práctica privada de su profesión.

Perteneció a un gran número de asociaciones profesionales e instituciones cívicas y culturales. Fue miembro del Ateneo de Puerto Rico. Fue Presidente de la Asociación Médica de Puerto Rico por dos años consecutivos. Además, presidió el capítulo de Puerto Rico de la Sociedad Americana de Cáncer, sociedad que le confirió la medalla de servicios distinguidos en el 1951. Presidió el Tribunal Examinador de Médicos durante 8

años y perteneció al mismo por 8 años más. Fue arduo colaborador del fenecido Dr. Isaac González Martínez en la cruzada y lucha contra el cáncer. Colaboró con muchas instituciones médicas del gobierno y al morir ocupaba el cargo de Director Médico del Hospital Oncológico de la Liga Puertorriqueña Contra el Cáncer. Su lucha en bien del paciente puertorriqueño que sufre de esta enfermedad es bien conocida y el mejor reconocimiento por esta particular labor está en los cientos de personas que fueron cuidadas y curadas por el doctor Oliveras Guerra.

Lo más admirable de la vida de este distinguido galeno puertorriqueño fue su gran generosidad, su dedicación a la medicina, la magnanimidad que tenía hacia aquellos que trataban de hacerle pasar momentos amargos en su vida, la sencillez y humildad de su alma y que sus hechos y toda su vida reflejaban la idea que el escritor francés Lamartine expresó: "que no quiere dejar tras de sí ninguna palabra hostil contra nadie. La posteridad no debe ser la cloaca de nuestras pasiones, debemos considerarla como la urna de nuestros recuerdos y no depositar en ella más que perfumes."

Hace 14 ó 15 años que el General McArthur, después. de ser relevado de su cargo como Jefe de las Fuerzas de las Naciones Unidas en Corea por el Presidente Truman, habló ante el Congreso de los Estados Unidos y dijo aquella frase que hoy día es famosa: "An old soldier never dies, he simply fades away." ("Un viejo soldado nunca muere, solamente desaparece lentamente"). En estos momentos podríamos decir en relación al doctor Oliveras Guerra: "Un viejo médico nunca muere, pero, aunque desaparece físicamente, su espíritu y su obra quedan con nosotros."

El doctor Oliveras Guerra no se ha ido. Fue parte de una obra grande y Puerto Rico la ha heredado. Gran parte de su ser lo dejó en el magnífico Hospital Oncológico Dr. I. González Martínez, el cual él luchó por fundar, construir y mejorar; gran parte de él vive en su hijo, que está siguiendo sus pasos como gran cirujano y profesor de nuestra Escuela de Medicina y mucho de él vive en sus nietecitas.

No es nada más justo que el haber dado el nombre de este distinguido puertorriqueño a este magnífico dispensario médico que servirá principalmente al tipo de paciente que tanto él quería: el paciente de pocos recursos económicos. Por eso deseo felicitar a aquellas personas que tuvieron tan feliz idea.

Para finalizar, deseo mencionar que en febrero de 1880, el poeta R. del V., ante la tumba del inolvidable puertorriqueño Don José Gautier Benítez, recitó un bello poema que terminaba diciendo:

"Al pie del sepulcro yerto,
al evocar tu memoria,
confuso y torpe, no acierto
si habré de llorar al muerto
o habré de cantar su gloria."

En estos momentos de honda emoción, no me parece que debo estar ni confuso ni torpe, pero sí, aunque lloro la ausencia del doctor Oliveras, al mismo tiempo le doy las gracias de todo corazón al Todopoderoso por haber hecho posible, que Artajerjes Oliveras Guerra viviera en ésta, nuestra época.

EDITORIAL

EDUCATION OF THE DIABETIC

Chronic diseases are the predominant disablers and killers in Puerto Rico as well as in the mainland. The improvement of the medical care in Puerto Rico has increased the span of life. In 1940 the average span of life in our island was 46 years while in 1962 was 69 years.

Diabetes mellitus is a chronic disease. Its prevalence rate increases rapidly with age, reaching a peak in the 65 to 80 age group (1, 2, 3). Among persons with diagnosed diabetes mellitus under 45 years of age the prevalence rate is 2.5 per 1,000 population, for those 45 or over the rate jumps to 27.6 per 1,000 (4). The older the individual gets, the higher are the chances of developing the disease if there is some inherited predisposition.

Screening programs have been conducted for many years by our Department of Health with the aim of diagnosing early the hidden diabetic. The American Diabetes Association has been conducting these screening programs for the past 20 years and in the Diabetes Week held for the first time in Puerto Rico in November 12-18, 1967, mass screening programs were conducted sponsored by the Puerto Rico Medical Association, the School of Medicine and the Department of Health. Thus, attempts are being made to make an early diagnosis of diabetes mellitus in our population.

An early detection of diabetes mellitus is of meager value if concurrently we do not plan an education program for the diabetic. The aim of all physicians who have diabetic patients under their care should be to keep them in the best possible health for the longest time (5). This is not possible unless the diabetic learns about the nature of his disease, the principles of its treatment, the degenerative complications of the disease, the complications of therapy and the relation of heredity to the disease. With understanding and knowledge the patient is better able to cooperate with his physician to achieve good control of his disorder. The diabetic needs motivation besides a genuine desire to keep in good health. Is up to us physicians to provide that initial motivation which will stimulate the patient to seek further information on his own. For the latter, numerous pamphlets and booklets are published by the American Diabetes Association and the U. S. Public Health Service (6, 7). Similar booklets are

betics had family histories of diabetes 2 to 10 times as often as the nondiabetic controls.

The majority of diabetics reporting in the survey were first- or second-generation diabetics. Approximately 17 percent of diabetics had diabetic mothers, and about 8 percent had diabetic fathers. About one-fourth of those with siblings reported diabetic siblings, and 7 percent of parents reported diabetic children. Only 1 percent of the study population represented three generations of diabetics.

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Age at onset of diabetes is an important factor in the severity of the disease, the natural course which it follows, and the treatment required. In general, persons who develop diabetes in childhood are the most severely affected, not only by the diabetes itself but by other conditions which may develop concomitantly. They usually require insulin for treatment and their diabetes is more difficult to control than that of persons who develop diabetes later in life. On the other hand, persons who develop diabetes as adults generally have milder cases than those who have had diabetes since childhood, and some can be treated by diet alone.

It is difficult to determine onset of diabetes since it is not possible to ascertain how long diabetes has been present before the diagnosis is made. However, the diagnosis is most often made in the fifth and sixth decades.

Half of the diabetics were diagnosed between the ages of 45 and 64, about 21.8 percent between 25 and 44 years of age, and another 20.0 percent at ages 65 years or later. Only 7.7 percent of the diabetics were diagnosed before their 25th birthday and 4.1 percent before age 15.

The majority of diabetics (80.1 percent) had two or more chronic conditions, i.e., at least one chronic condition in addition to diabetes. Over half of them (57.9 percent) reported three or more chronic conditions.

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Those reported most often were heart conditions (21.1 percent), hypertension (16.8 percent), and impaired vision (10.3 percent). However, if the two condition groups, impaired vision and blind in both eyes, were combined to represent all visual impairments, this category would then have the second highest frequency of reporting (16.9 percent).

Most of the conditions were overrepresented among females, in most cases by a ratio of at least two to one. Three of the conditions, however, were clearly characteristic of male diabetics, the absence of fingers or toes, the absence of major extremities, and tuberculosis.

The percent of diabetics reporting these conditions who were male were, respectively, 76.5, 63.6, and 72.7 percent. Two other conditions, paralysis and vascular lesions of the central nervous system, were reported about equally by each sex (part of the apparent variation was due to rounding).

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About three-fourths of the diabetics reported that at the time of the survey they were taking some medication for diabetes. The largest proportion, 48.4 percent, were taking oral drugs; 25.7 percent were taking insulin. Another 2.0 percent were taking both oral drugs and insulin. The remaining 24.0 percent took neither.

There was considerable variation by age in type of medication taken, reflecting the known differences in treatment of adult and

juvenile diabetics. (Insulin is prescribed for the majority of juvenile diabetics, whereas oral drug are prescribed primarily for adults.) A very high proportion of persons under 25 years of age (67.6 percent) took insulin—two to three times the proportion in any other age group. Persons 45 years and older most often took oral drugs. Diabetics between 25 and 44 years of age equally often took oral drugs and insulin. They were somewhat overly represented among those taking neither.

Xanthinuria

Xanthinuria is a very rare disorder characterized by deficient production if uric acid, a major end product of the metabolism of purines derived from dietary protein. Public Health Service scientists have shown that xanthinuria results from the absence of an enzyme, xanthine oxidase, that generates uric acid from hypoxanthine and xanthine, both intermediate compounds in purine metabolism.

In patients with xanthinuria, the metabolic block in uric acid production causes the accumulation of hypoxanthine and xanthine in the blood. The excess is excreted by the kidneys; but, because both compounds are only sparingly soluble in urine, they may crystalize out of solution to form kidney stones. This appears to be the only potentially serious consequence of the disorder. Stone formation can usually be avoided if the patient drinks plenty of water and avoids glandular meats and other high-purine foods.

There are only 7 or 8 known cases of xanthinuria in the world. One of these is presently a study patient at the Clinical Center of the National Institutes of Health.

The investigators found that the blood uric acid level in this patient was only 0.5 milligrams per 100 milliliters of plasma (normal range: 3.5 - 6 mg/100 ml). Her daily urinary excretion of uric acid was 6 mg., whereas the normal excretion rate is 250-600 mg. per day. These findings indicated that the patient was either destroying uric acid by some abnormal metabolic process or else was not producing it at a normal rate.

Subsequently the scientists devised new, extremely sensitive techniques to measure the activity of the enzyme xanthine oxidase in human tissues. The tissues of the patient with xanthinuria exhibited no detectable xanthine oxidase activity.

The studies have not only clarified the nature of the metabolic defect underlying xanthinuria, but may also have relevance in newer therapeutic approaches to a very common disorder of purine metabolism: gout. In gout, the problem is excessive uric acid production. The excessive blood levels of uric acid may result in deposition of uric acid crystals in the joints.

Earlier therapy to prevent recurrent attacks of gout involved the use of drugs to hold blood levels of uric acid down by increasing urinary excretion of uric acid. However, a new drug called allopurinol reduces blood uric acid levels by blocking its production from xanthine and hypoxanthine. It does so by inhibiting the enzyme xanthine oxidase.

Thus, while receiving allopurinol, these patients are made "xanthinuric." The resultant increase in blood levels and urinary excretion of hypoxanthine and xanthine raises the possibility of precipitation and kidney stone formation, although kidney stones

have not yet been a reported side effect of allopurinol therapy.

In any event, the rare patient with xanthinuria provides a living model for gout patients receiving allopurinol on a long-term basis.

These findings were reported at the recent annual meeting of the American Association of Clinical Chemists by Dr. Karl Engelman, of the National Heart Institute's Experimental Therapeutics Branch.

Drs. Richard W.E. Watts, James R. Klinenberg, Albert Sjoerdsma, and J. Edwin Seegmiller participated in these studies with Dr. Engelman.

Influenza Vaccine and Amantadine*

The Commitee on Control of Infectious Diseases has reviewed three developments with respect to viral influenza which require practical decisions of the pediatric practitioner. Its recommendations follow:

1. Despite prediction of an increased prevalence of influenza A2 infections in the upcoming season, routine influenza immunization is not recommended for normal children.
2. Individuals in high risk groups should receive vaccine this year, and the bivalent rather than the polyvalent vaccine is the preparation of choice.
3. At this time, the use of amantadine is not recommended for children except those in study populations.

Prediction of Increased Prevalence A2 Influenza

The Public Health Service Advisory Committee on Immunization Practices has noted that susceptibility to A2 influenza viruses is relatively high, especially in the Eastern U.S. Because of low prevalence in recent years, we may expect a *substantial* number of cases.

Some health officers have recommended broad-scale immunizations. However, the Committee *recommends influenza immunization only for children known to experience high morbidity or mortality from influenza,* including those with the following:

a. Rheumatic heart disease, especially those with mitral stenosis.
b. Other cardiovascular disorders such as congenital or hypertensive heart disease, especially those with evidence of frank or incipient cardiac insufficiency.
c. Chronic bronchopulmonary diseases — for example, cystic fibrosis of the pancreas, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis, and patients with weak or paralyzed respiratory muscles.
d. Chronic metabolic disease.
e. Chronic glomerulonephritis or nephrosis.
f. Chronic neurologic disorders.

Revised Formulation of Vaccines

To be of value, an influenza vaccine must contain strains which are antigenically similar to those which will be encountered in the season following vaccine administration. Usually these are strains recovered in the recent past rather than the distant past.

Further, the total number of units of influenza antigen to be included in a single dose is limited because of the potential toxicity. Therefore, many feel that the most practical formulation of vaccine is one including greater amounts of two or three

* *Published with permission of the American Academy of Pediatrics.*

recent strains rather than a smaller amount of each of 4 or 5 strains.

Two formulations of the vaccine are now available.

Polyvalent (A, A_1, A_2 and B Strains) — 1967

Type	*Strain*	*CCA Units/ml*
A	PR/8/34	100
A_1	Ann Arbor/1/57	100
A_2	Japan/170/62 100)	
	)	200
	Taiwan/1/64 100)	
B	Massachusetts 6/3/66	200
	Total	600

Bivalent (A_2 and B Strains) — 1967

Type	*Strain*	*CCA Units/ml*	
A_2	Japan/170/62	150)	
		)	300
	Taiwan/1/64	150)	
B	Massachusetts 3/66		300
			—
	Total		600

The bivalent vaccine is the choice for those infants and children requiring protection this year. Those never vaccinated or not vaccinated since July 1963 should receive a primary immunization series of bivalent vaccine. (see Table.) The primary series consists of an initial subcutaneous dose, followed by a second two months later. It may be noted that even a single dose can afford some protection. A second injection as early as two weeks after the first one will enhance the antibody response.

Children vaccinated after July 1963 require only a single booster of bivalent vaccine.

*Dosage Schedule for Influenza Vaccine Innoculations**

	Not Previously Vaccinated			*Vaccinated Since 1963*	
	Volume (ml)	*No. of* Doses	*Interval*	*Volume* (ml)	*No. of* Doses
Adult	1.0	2	2 mos.	1.0	1 per yr.
Child 6-12 yrs.	0.5	2	2 mos.	0.5	1 per yr.
Child, 3 mos.— 5 yrs.**	0.1 or 0.2	3	2 mos.	0.1 or 0.2	1 per yr.

* *Route: subcutaneous. Timing: vaccination schedule to be completed by mid-December. Begin as soon as practical in the fall.*
Containdications: hypersensitivity to egg proteins.

** *Acetylsalicylic acid (60 mg per year of age) every 6 hours for first 24 hours advised to prevent or minimize febrile reaction in this age group.*

Amantadine (Symmetrel®)

Amantadine hydrochloride is a synthetic compound reported to be useful in the chemoprophylaxis of influenza A2 infection. *The Committee does not recommend its use for children* for the following reasons:

a. The drug has not been widely studied in children.
b. Reported effectiveness of the drug is limited to influenza A2 virus infections.
c. The drug must be administered prior to infection, and specific virus diagnosis in anticipation of exposure is impractical.
d. Toxic manifestations have occurred at dosage only 100-200 mg greater than that recommended.

NOTICIAS

Locales

REUNIONES

Feb. 2-4—Convención Anual de la Academia Americana de Práctica General.

Feb. 6-10—Convención Anual de la Sección de Pediatría de la Asociación Médica de Puerto Rico.

PLAZAS VACANTES

El Departamento de Salud informa que tiene una serie de plazas de médico disponibles en distintas categorías y pueblos de Puerto Rico, para trabajar con el gobierno.

Los interesados deben comunicarse con el Dr. José F. Rechany, Ayudante Especial del Secretario de Salud.

INTERNADO EN MEDICINA EN EL HOSPITAL DE VETERANOS

Recientemente recibió la aprobación por el "Council on Medical Education" de la Asociación Médica Americana un nuevo programa de entrenamiento para internos en medicina (Straight Medical Internship) en el Hospital de Veteranos de San Juan. El programa se inaugura en enero 1ro., 1968.

El programa de un año incluirá dos trimestres de trabajo en las salas de medicina del Hospital de Veteranos, tres meses en las salas de mujeres del Hospital Universitario y un trimestre de trabajo electivo a elección del individuo. Durante este último período el interno puede permanecer en el Servicio de Medicina dedicándose al estudio de una sub-especialidad o pasar a los Servicios de Cirugía, Laboratorio, Rayos-X, Medicina Física en el Hospital de Veteranos, o a los Servicios de Pediatría u Obstetricia-Ginecología del Hospital Universitario.

El interno recibirá su entrenamiento bajo la supervisión de residentes y médicos especialistas en cada rama. El entrenamiento ha sido aprobado por el Comité del Decano de la Escuela de Medicina y está íntimamente integrado con los programas de enseñanza del Hospital Universitario.

El salario anual será de $4,725.00.

Para más detalles el interesado debe dirigirse al Dr. Elí A. Ramírez, Jefe del Servicio de Medicina, Hospital de Veteranos, Ponce de León 520, San Juan, Puerto Rico, 00901.

RESIDENCIAS EN MEDICINA

El Hospital de Veteranos de San Juan tiene plazas de primero, segundo y tercer año para residencia en Medicina Interna.

Este programa está organizado en colaboración con el Departamento de Medicina del Hospital Universitario y la Escuela de Medicina de la Universidad de Puerto Rico. Está aprobado totalmente por el Comité Examinador de Residencias de la Asociación Médica Americana. Los salarios son como sigue:

Primer año	$5,985.00
Segundo año	$6,615.00
Tercer año	$7,245.00

Para mayor información, favor de dirigirse al Dr. Elí A. Ramírez, Jefe, Servicio de Medicina, Hospital de Veteranos, Ponce de León 520, San Juan, P. R. 00901.

NEW BOOKS

Other books received by the University of Puerto Rico School of Medicine and School of Dentistry.

Anatomy:

1. Ciba Foundation Study Group No. 23, London, 1965. Egg implantation. Boston, Little, Brown and Co., 1966. QS645.

2. International Anatomical Nomenclature Committee. Nomina anatomica. 3d ed. Amsterdam, Excerpta Medica Foundation, 1966. QS15

3. Lockhart, Robert Douglas. Anatomy of the human body. Philadelphia, Lippincott, 1959. QS4

Chronic Illness, Geriatrics:

1. Carter, Howard Wesley. The aged and chronic disease; research in a local health department. Jacksonville, Florida, 1966. WT20

2. International Social Security Association. Volume and cost of sickness benefits in kind and cash. Present state of the survey on the volume and

cost of sickness benefits in kind and cash for the years 1959 to 1962. Report...Geneva, 1965. WT30

3. Symposium for Medical Educators. Long term care and preventive medicine: a symposium for medical educators. St. Louis, Jewish Hospital, 1966. WT500

Physiology:

1. International Summer School of Molecular Biophysics, Squaw Valley, Calif., 1964. Molecular biophysics. New York, Academic Press, 1965. QT34

2. Symposium on the Principles of Biomolecular Organization. Ciba Foundation Symposium: Principles of biomolecular organization. Boston, Little, Brown and Co., 1966. QT34

Nursing:

1. Cape, Barbara F. Guía-diccionario del auxiliar sanitario y de la enfermera. Barcelona, Elicien, 1966. WY13

2. Jensen, Deborah (MacLurg) The principles and practice of clinical instruction in nursing. 2d ed. St. Louis, Mosby, 1946. WY18

3. U. S. Public Health Service. Closed drainage of the chest, a programmed course for nurses. Washington, D.C., 1966. WY161

4. U. S. Public Health Service. Nursing care of the aged, an annotated bibliography for nurses. Arlington, Virginia 1967. SERIAL

Dentistry:

1. American Association of Dental Schools. Report of dental education summer internship program for graduate education and psychology students, 1966. WU18

2. Cifuentes Aguirre, Oscar. Odontología y mutilaciones dentarias mayas. Guatemala, Editorial Universitaria, 1963. WU11

3. Clark, J. Stanley. Open wider please, the story of dentistry in Oklahoma. Norman, Oklahoma, University of Oklahoma, 1955. WU11

4. College Publishing Corporation, Brooklyn. How to pass dental aptitude test; questions and answers. 3d ed. Brooklyn, 1966. WU18

5. Conference for Teachers of Dental Materials. Proceedings. Chicago, Northwestern University Dental School, 1966. WU190

6. Conference on Training Dental Students to use Chairside Assistants. Proceedings. 1st-3rd-4th. Chicago, Ill., 1960-63. WU18

7. Current therapy in dentistry. St. Louis, Mosby Co., 1964-66. WU166

8. Elwell, Kenneth R. Classification and appraisal of objections to fluoridation. Ann Arbor, Michigan, The University of Michigan, 1960. WU270.

9. European Organization for Research on Fluorine and Dental Caries Prevention. Congress, 11th, Sandefjord, Norway, 1964. Advances in fluorine research and dental caries prevention. v. 3; proceedings. Oxdord, Pergamon Press, 1965. WU270

10. Febres-Cordero, Foción. Orígenes de la odontología. Caraças, Editorial Arte, 1966. WU11

11. Fédération Dentaire Internationale. A lexicon of English dental terms with their equivalents in Español, Deutsch, Francais, Italiano. The Hague, Holland, A. Sijthoff, 1966. WU13

12. Horowitz, Sidney L. The nature of orthodontic diagnosis. St. Louis, Mosby, 1966. WU400

13. Jarabak, Joseph R. Management of an orthodontic practice. St. Louis, Mosby, 1965. WU400

14. Schroeter, Charles. The dentition of man; an atlas of tooth morphology. Seattle, University of Washington Press, 1966. WU101

15. Seminar on Social Dentistry. Proceedings. Washington, D.C., Public Health Service, 1964. W113

16. Shapiro, Max, ed. The scientific bases of dentistry. Philadelphia, Saunders, 1966. WU100

17. U. S. National Institute of Dental Research. Who' who in N.I.D.R. Bethesda, Maryland, 1967. WU22

18. U. S. Public Health Service. Division of Dental Public Health and Resources. Organizing a dental assistant training program. 1965. WU90

19. Weinberg, Lawrence A. Atlas of crown and bridge prosthodontics. St. Louis, Mosby, 1965. WU-515.

20. Woodstock Workshop on Dental Health Education 1966. Proceedings of a New England conference on dental health education. Vermont, New England Council on Dental Health and Care, 1966. WU18

21. Young, Wesley, O., ed. The utilization of fluorides applied topically for the prevention of dental caries. Lexington, Kentucky, Dept. of Community Dentistry, 1966. WU270

22. Zepeda, Carlos N. Mi concepto sobre protesis dental. San Salvador, Rep de El Salvador, 1945. WU500

Hospitals:

1. American Medical Association. Emergency department, a handbook for the medical staff. Chicago, 1966. WX215

2. A Balanced teaching hospital. Ondon, N.Y., Published for the Nuffield Provincial Hospitals Trust by the Oxford Univ. Press, 1965. WX28FA1

3. Bennett, Addison C. Methods improvement in hospitals. Phila., Lippincott, 1964. WX150

4. Hospital policy decisions: process and action. N.Y., Putnam, 1966. WX150

5. Huffman, Edna K. Manuel for medical record librarians. Rev. 5th ed. Berwyn, Ill., Physicians' Record Co., 1963. WX173

6. Llewelyn-Davies, R. Hospital planning and administration. Geneva, World Health Organization, 1966. WX150

7. Pittsburgh. University. Health Law Center. Student's guide to hospital law. Pittsburgh, 1960. WX32

Nervous System:

1. Critchley, MacDonald. Developmental dyslexia. Springfield, Ill., Thomas, 1964. WL340

2. National Clearinghouse of Mental Health Information. Bibliography on religion and mental health, 1960-1964. Washington, D.C., 1967. ZWM-61.

3. Nobel Symposium. 1st, Sodergarn, Sweden, 1965. Muscular afferents and motor control; proceedings. N.Y., Wiley, 1966. WL102

4. Remmen, Edmund. Psychochemotherapy. Los Angeles, Calif., Western Med. Pub., 1962. WM400

5. Rinkel, Max, ed. Biological treatment of mental illness. New York, L.C. Page, 1966. WM-400

6. Roselló, Juan A. Psicología de las organizaciones. Washington, D.C., San Juan, Puerto Rico, Departamento de Psiquiatría, 1967. BF636

7. Symposium on suicide. Washington, D.C., School of Medicine, George Washington University, 1966. WM207

8. U. S. Army Medical Service. Historical Unit. Neurological surgery of trauma. Washington, Office of the Surgeon General, Dept. of the Army, 1965. WL368

Public Health:

1. Bernzweig, Eli P. Legal aspects of PHS medical care. Wash., U. S. Dept. of Health, Education, and Welfare, 1966. WA32AA1

2. Blum, Henrik, L. Public administration—a public health viewpoint. N. Y., Macmillan, 1963. WA525.

3. Cox, Charles R. Práctica y Vigilancia de las operaciones de tratamiento del agua. Ginebra, Organización Mundial de la Salud, 1966. WA690

4. U. S. Appalachian Regional Commission (ARC) Health Advisory Committee. Report. Washington, D.C., 1966. WA900

5. U. S. Public Health Service Proceedings of the 2d Joint Meeting of the Clinical Society and Commissioned Officers Association of the U. S. Public Health Service. Atlanta, Georgia, 1967. ZWA100

Radiology:

1. Blatz, Hanson. Introduction to radiological health. New York, McGraw-Hill. 1964. WN610

2. Ingram, Marylou, comp. Biological effects ionizing radiation, an annotated bibliography, covering the years 1898-1957. N.Y., U. S. Atomic Energy Commission, 1966. ZWN610

3. Symposium on Health Physics in Biology and Medicine. San Juan, University of Puerto Rico. 1959. WN100

4. World Health Organization. Methods of radiochemical analysis. Geneva, 1966. WN415

5. Workshop on Wound Healing. Proceedings of a workshop... 1963... Washington, National Academy of Sciences, 1966. WO185

Cardiovascular System:

1. Cowdry's arteriosclerosis. 2d ed. Springfield, Ill., Thomas, 1967. WG550

2. Kaplan, H. S. Congenital heart disease. 2d ed. N.Y., Blakiston Div., McGraw-Hill, 1965. WG-220

3. National Congestive Heart Failure Seminar. Report and recommendations of the...seminar. Berkeley, Calif. State, Dept. of Public Health, 1967. WG370

4. U. S. Dept. of Health, Education and Welfare. Vocational Rehabilitation Administration. Heart disease, cancer, stroke. Selected characteristics of clients rehabilitated in State Vocational Rehabilitation Agencies, fiscal year 1965. WG200

Space Medicine:

1. International Symposium on the Physics and Medicine of the Atmosphere and Space. 2d, San Antonio, 1958. Physics and medicine of the atmosphere and space. New York, Wiley, 1960. WD-700

Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Feb. 5-9—Psychiatry and the Internist, University of Southern California School of Medicine, Los Angeles, California.

Feb. 28-March 2—Hypertensive Cardiovascular Diseases: Mechanism and Treatment. Clinical Research Institute of Montreal, Montreal, P. Q., Canada.

Mar. 14-16—The Clinical Selection of Patients for Cardiac Surgery. University of Minnesota, Rochester, Minnesota.

Mar. 18-22—Psychiatry and the Internist: Albany Medical College of Union University, Albany, N. Y.

Mar. 28-30—Current Concepts in Physiology of Respiration, Circulation and Electrolyte Metabolism, to be held at The Somerset Hotel, Boston, Mass.

Apr. 22-26—Clinical Endocrinology — Recent Advances in Diagnosis and Treatment. Mayo Graduate School of Medicine (University of Minnesota) and Mayo Clinic, Rochester, Minn.

May 12-15—Frontiers in Gastroenterology. University of Pennsylvania School of Medicine, to be held at The Bellevue Stratford Hotel, Philadelphia, Pa.

OTHER MEETINGS

Jan. 18-20—National Conference, *"The Community and Emergency Medical Services,"* to be held in San Francisco Hilton Hotel, San Francisco, California.

Jan. 11-13—AMA Committee on Maternal and Child Care *"First International Conference on Prematurity",* to be held in Ft. Lauderdale, Florida.

April 4-6—Third National Conference on Health Education of the Public, Pick-Congress Hotel, 520 S. Michigan Ave., Chicago, Ill., 60605.

AMDOC

AMDOC (short for AMerican DOCtor) is a non profit corporation. It is not a government agency. AMDOC is not religiously oriented. It is a person-to-person medical and educational service. AMDOC arranges assignments in foreign medicine. AMDOC's roster of hospitals in foreign areas contains numerous requests for general practitioners, specialists and allied personnel. Their skills are acutely needed in locations in Central and South America, the Far East, Southeast Asia and Africa.

AMDOC receives applications from physicians, dentists and allied personnel for foreign assignments. They offer to serve as volunteers for periods from one month to three months or longer without compensation. They finance their own transportation. Their motivation may be a desire for broader experience or for giving of themselves, or both. It can be a challenging, rewarding and exhilarating experience. It is also fun. AMDOC encourages family participation as a means of education in basic international human understanding.

AMDOC assignments are acceptable for educational credit by the American Academy of General Practice.

Ask Dennis G. Karzag, Executive Secretary of AMDOC, 27 East Cañón Perdido Street, Santa Bárbara, California 93101, for more details and copy of AMDOC's publication which informs its readers of current programs and reports of physicians returning from abroad.

RESIDENT LOAN FUND

The Resident Loan Fund was established by the American College of Chest Physicians to assist young physicians in taking postgraduate training in the specialty of diseases of the chest. Any qualified resident may apply for a loan by writing to the Comittee on Resident Loan Fund in care of the Executive Offices of the College. All applications must be approved by the Committee before a loan can be granted.

The total amount of a loan to any individual in any one year may not exceed $1,500.00 and, except under special circumstances, the loan will be made available on the basis of $125.00 per month. No individual may borrow more than $4,500.00. All loans must be protected by life insurance, the

premiums to be paid by the borrower.

Interest on the loan is charged at the rate of 3% per annum. Neither principal nor interest on the loan need to be repaid for a period of three years after the date of the first loan advance, provided the physician is continuing his postgraduate training in diseases of the chest.

MEMBERS OF THE AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS REPORT ON SAFETY OF ORAL CONTRACEPTIVES

The most extensive survey to date on the use and effects of oral contraceptives will be released to the public October 24 by McCall's magazine. Over 6,700 members of The American College of Obstetricians and Gynecologists participated in the study, the first ever made in conjunction with the College. The College membership was informed of the survey results in the October issue of the ACOG NEWSLETTER distributed last week. The survey report brings together for the first time the collective observations of the specialists who have had the broadest experience with oral contraceptives.

Details of the authoritative study, particularly the benefits and risks of oral contraceptives, are revealed in McCall's forthcoming article. Possible physical side effects of the pill were explored at length in the study, as well as psychological effects.

An unprecedented 90 percent of the 8,522 Fellows answered a detailed questionnaire on the pill, prepared by The American College of Obtetricians and Gynecologists. Replies from 79 percent — 6,733 specialists in the United States and Canada — were analyzed by computer and the results compiled by McCall's.

The results of the survey show ninety-five percent of the specialists feel oral contraceptives are safe enough to prescribe for their patients and eighty-seven percent give it more frequently than any other family-planning method. Patients request the pill over every other contraceptive method, reported ninety-six percent of the physicians surveyed. "The survey revals an overwhelming acceptance of the pill by the College," says Dr. John S. Lyle, chairman of the ACOG's Committee on Public Education.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

ANUNCIOS

OFICINA PARA ALQUILAR O VENDER

Por motivos de estudio rento o vendo a médico generalista oficina equipada en sitio céntrico (Avenida Roosevelt 1129, Puerto Nuevo, Puerto Rico).

Para más detalles, favor de comunicarse con el Dr. José Rafael Rivera después de las 6:00 p.m. en el teléfono 783-4843. Pueden también solicitarle personalmente en el Departamento de Anestesiología del Centro Médico de Río Piedras.

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La SSS —Seguros de Servicios de Salud— es la más completa protección médica para personas y familias de **todos** los niveles económicos. Usted sólo paga una módica prima ajustada a sus ingresos. Pero, en caso necesario, recibe al momento todos los servicios indispensables con el médico, hospital o laboratorio de su selección. La SSS pone a su disposición todas las ventajas de la medicina privada, a través de 1056 médicos participantes, 34 hospitales y 65 laboratorios. Algunos de nuestros planes incluyen hasta servicios dentales, con 269 dentistas asociados. Para más detalles, llene el cupón que publicamos aquí y envíelo a la dirección que aparece en el mismo. También puede visitar nuestras oficinas o llamar a los teléfonos 765-3232 en San Juan, 842-7367 en Ponce.

SSS, Apartado 3628
G. P. O.
San Juan, P.R. 00936

Señores:
Favor de enviarme detalles adicionales sobre los planes SSS y sus beneficios para mí.

NOMBRE _____

DIRECCION _____

_____
(Calle y número, o apartado)

CIUDAD O PUEBLO _____ ZIP CODE _____

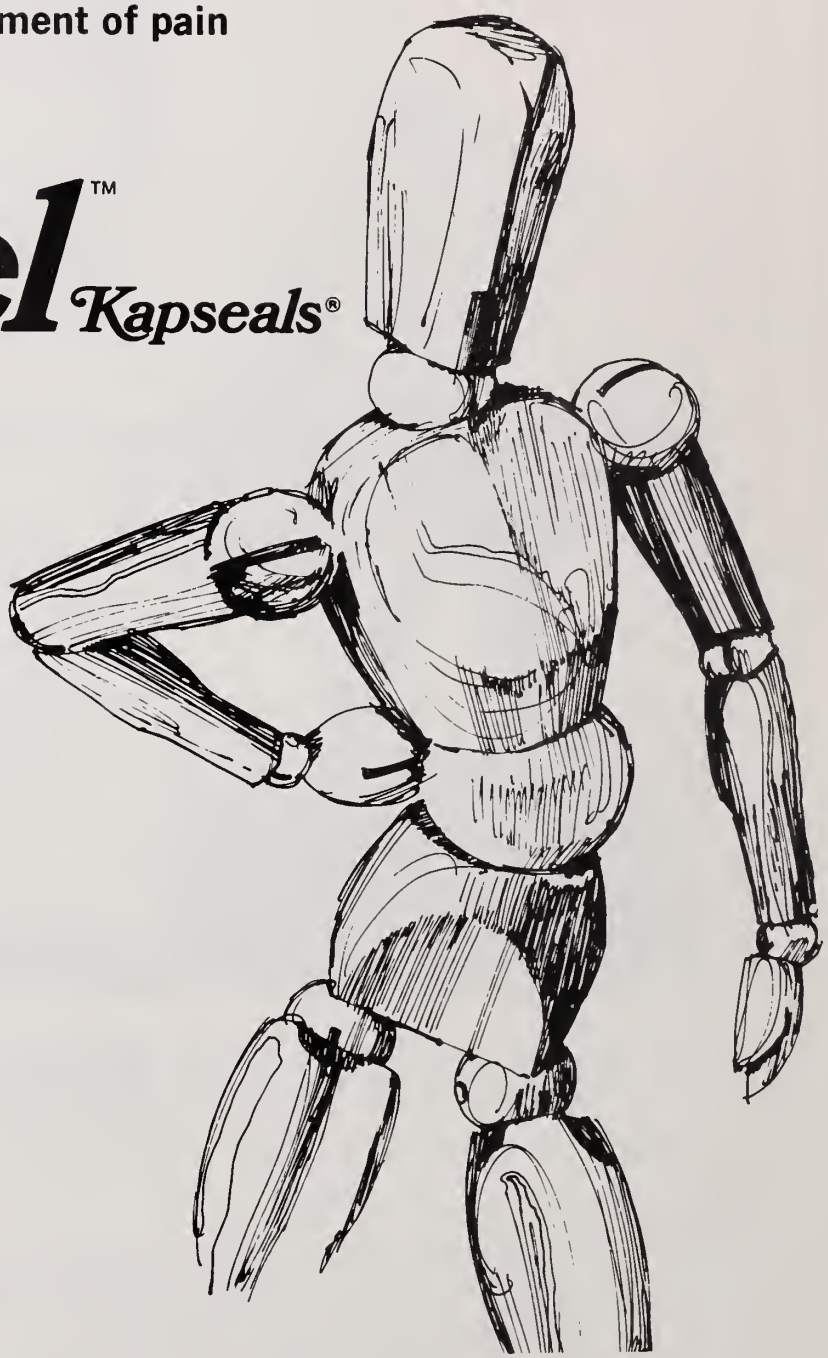
LA SSS LE DA TRIPLE SEGURIDAD — Salud protegida a diario. Servicios de primera. Salvaguardia económica.

:W . . . for effective management of pain

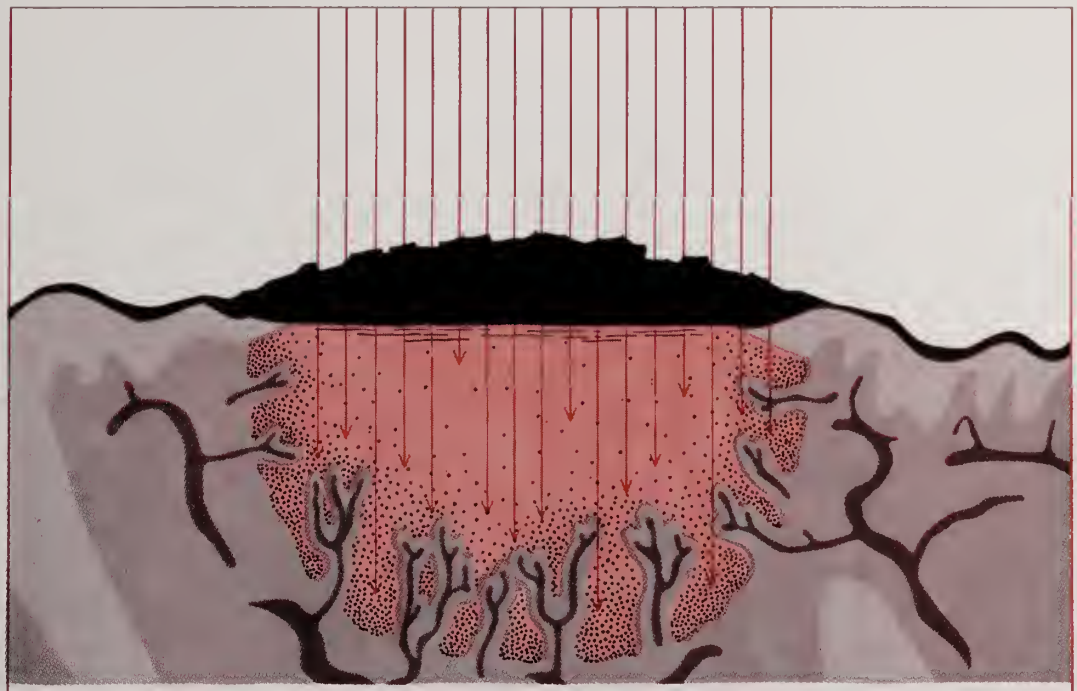
Ponstel™ Kapseals®

nefenamic acid)

nnarcotic oral analgesic



PARKE-DAVIS



Why the Enzymes?

Many skin infections lie hidden under crusts, debris and necrotic tissue. CHYMAR® Ointment provides a powerful enzyme formulation which breaks down this natural barrier and ensures full penetration of the hydrocortisone and neomycin for rapid and effective *anti-inflammatory* and *antibiotic* action.

The water-miscible base in CHYMAR Ointment also promotes maximum release of its therapeutic agents at the site of the infection. **CHYMAR Ointment is most effective for comprehensive topical treatment of all infected and inflammatory skin lesions.**

R Supplied ir 1/6 oz. tubes.

CHYMAR®

(Proteolytic enzymes, hydrocortisone and neomycin)

Ointment

ARMOUR PHARMACEUTICAL COMPANY Chicago, Illinois 60690, U.S.A.


in moderate hypertension and
poorly controlled mild hypertension
(when diuretics or sedatives are inadequate, for example)

When your patients expect a lot...

like relief from hypertensive symptoms
(headache, fatigue, nervousness, palpitation or insomnia, for example)

like an up-to-date, once-a-day dosage schedule
(a schedule not unlike timed-release medication, for example)

like a daily dose of medication for peanuts
(at 10¢ a tablet, for example)

like generally well-tolerated therapy
(as described in the package insert, for example)

...give them a little
(one tablet daily)

Regroton®

chlorthalidone 50 mg., reserpine 0.25 mg.

Indications: Hypertension. **Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. **Warning:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Regroton should be used in pregnant patients or in women of childbearing potential only when, in the judgment of a physician, its use is deemed essential to the welfare of the patients; adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Regroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue Regroton therapy two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, Regroton should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. **Adverse Reactions:** The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. **Average Dosage:** One tablet daily with breakfast. **Availability:** Pink, single-scored tablets in bottles of 100 and 1000. (B) 46-600-B
For details, see complete Prescribing Information.

Geigy Pharmaceuticals, Division of
Geigy Chemical Corporation, Ardsley, N.Y.

Geigy



NORPRAMIN
(clorhidrato de desipramina)

el ANTIDEPRESIVO
no-sedante de acción rápida

vence el abatimiento, levanta el ánimo, restablece la confianza

La depresión frecuentemente se caracteriza por sentimientos de culpabilidad, inutilidad, desolación y privación. Estas manifestaciones, acompañadas de síntomas tales como insomnio, malestar, tristeza y recelo, responden rápidamente al NORPRAMIN (clorhidrato de desipramina). La mejoría generalmente se manifiesta 2 a 5 días después de iniciado el tratamiento; algunas veces antes. Los pacientes con sensibilidad comprobada a estimulantes del sistema nervioso central, pueden experimentar excitación al desaparecer su depresión; en estos casos se sugiere reducir la dosis o administrar simultáneamente tranquilizantes.

Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardiacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

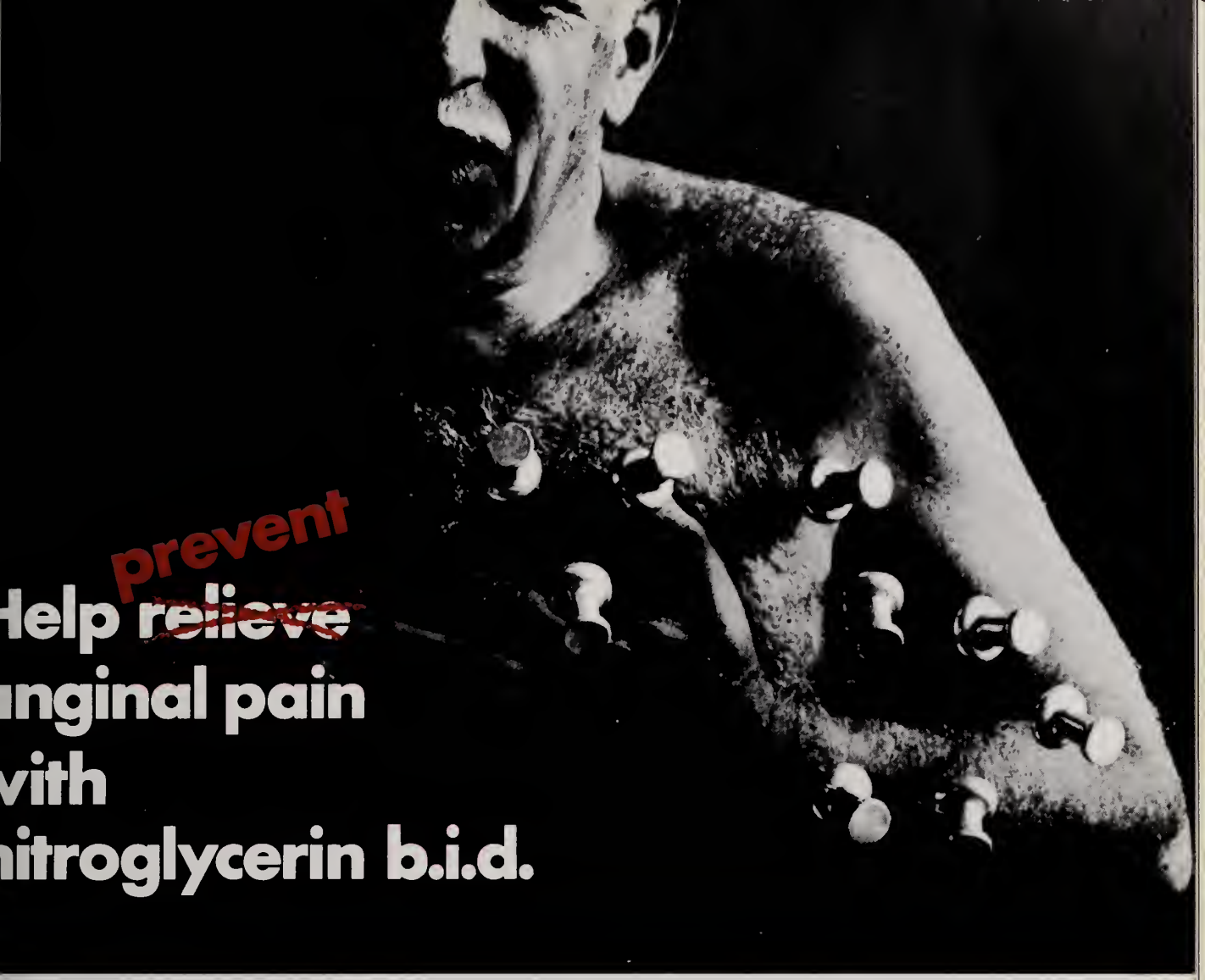
Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extrapiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

LAKESIDE

PRODUCTOS
PARA PACIENTES
QUE USTED
VE A DIARIO

Lakeside Laboratories, Inc. Milwaukee, Wisconsin 53201—EE.UU.

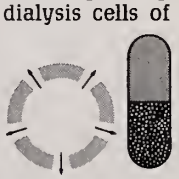


Unique Nitrospan micro-dialysis process* adds an important dimension–TIME–to nitroglycerin therapy

elps decrease frequency and severity of attacks; often creases exercise tolerance. Decreases need for sub-gual nitroglycerin, increases patient confidence. nooth, continuous release independent of gastrointes-al functions reduces headache and other side effects at might result from peak concentrations of tablet or termittent-release preparations.

dication and Dosage: For prophylactic use only in an-na pectoris, 1 capsule every 12 hours. **Precautions:** For ophylaxis only, not for relief of acute anginal attacks. lerance to nitrites may develop on long-continued use. **ntraindications:** Idiosyncrasy to nitroglycerin, and rly myocardial infarction. **Side Effects:** With use of rites, transient headache, postural hypotension, nausea and vomiting may occur. Overdoses may cause flushing, dizziness, tachycardia, headache and syncope.

*The **micro-dialysis cell.** Nitrospan's timed-release mechanism is different from those usually employed in sustained-action capsules, which rely on unpredictable digestive processes. The nitroglycerin in Nitrospan capsules is contained within hundreds of dialysis cells of controlled permeability. The contents of each micro-dialysis cell are released by diffusion rather than disintegration, at a continuous rate independent of gastrointestinal action. Only the presence of fluid is required.



NEW from USV **NITROSPAN®** CAPSULES

brand of **nitroglycerin** 2.5 mg. in micro-dialysis cells

For a starter supply of NITROSPAN, write: USV PHARMACEUTICAL CORPORATION, 800 Second Avenue, New York, N.Y. 10017

PRODUCERS OF PBI® TD (chlorpromazine USV)



WHAT DOES GALVANIC SKIN RESISTANCE DEMONSTRATE ABOUT THE EFFECT OF VALIUM (diazepam)?

Galvanic skin resistance... one measure of the Valium (diazepam) effect in reducing the somatic response to acute stress[1,2]

The subjective value of Valium (diazepam) has been proved by many clinical and empirical evaluations. Now, also objective criteria such as used in other areas of scientific research have demonstrated the effectiveness of Valium (diazepam) in reducing certain somatic responses to acute stress.

Devised as a research tool in psychosomatic medicine, this interesting method records respiratory excursions, galvanic skin resistance, cardiac activity and finger pulse volume as physical responses to stress. These autonomic nervous system responses to a standardized stressor—a film dealing with life-threatening incidents—are continuously monitored on the polygraph.

This gives a graphic representation of changes which the body may undergo in reacting to stress. The application of modern statistical analysis to these graphs provides a yardstick by which the calming effect of Valium (diazepam) can be measured quantitatively.

Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Infants, patients with a history of convulsive disorders, glaucoma or known hypersensitivity to drug.

Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.

Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

Dosage—*Adults:* Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d. *Geriatric patients:* 1 or 2 mg/day initially, increase gradually as needed and tolerated. (See *Precautions.*)

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50 and 500.

Roche Laboratories, Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

References: 1. Selesnick, S. T., and Clemens, T. L.: From research film "Motion Picture Films in Psychosomatic Research," available from Roche Laboratories. 2. Clemens, T. L., and Selesnick, S. T.: *Dis. Nerv. System,* 28:98, 1967.

VALIUM® (diazepam) Roche®

useful for somatic symptoms of psychic tension

Now Available

New DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE 300mg FILM COATED TABLETS

It's made for b.i.d.

More and more physicians are taking the option of b.i.d. dosage with DECLOMYCIN...so stock this new dosage form they've been asking for. Remember...when doctors write for new DECLOMYCIN 300 mg tablets it means...

One mid-morning **One mid-evening**

the total daily dosage requirement and schedule for adults

Effective in a wide range of everyday infections —respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill —when the offending organisms are tetracycline-sensitive.

Side effects typical of tetracyclines include glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis, dermatitis, overgrowth of nonsusceptible organisms, tooth discoloration (if given during tooth formation) and increased intracranial pressure (in young infants). Also, very rarely, anaphylactoid reaction. Reduce dosage in impaired renal function. Because of reactions to artificial or natural sunlight (even from short exposure and at low dosage), patient should be warned to avoid direct exposure. Stop drug immediately at the first sign of adverse reaction. It should not be taken with high calcium drugs or food, and should not be taken less than one hour before, or two hours after meals.

Tablets: 300 mg of demethylchlortetracycline HCl.

CYANAMID BORINQUEN CORP., LEDERLE LABORATORIES DEPARTMENT, Santurce, P. R. Lederle

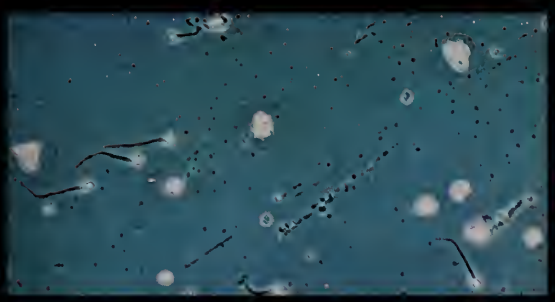
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

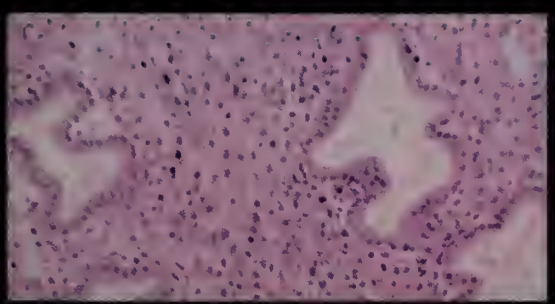
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.



Spermatozoa appear healthy, active, freemoving.

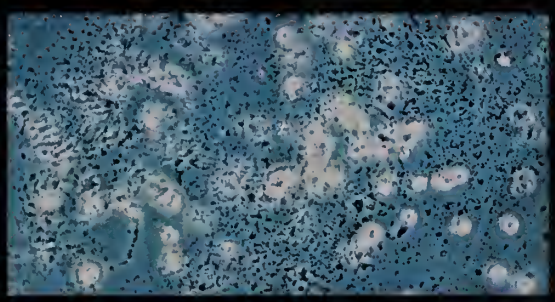


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

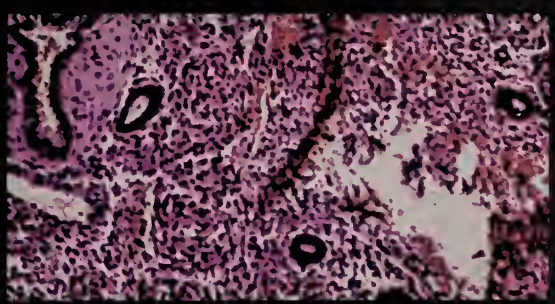
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous – with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

Norinyl®-1 tablets

(norethindrone 1mg ē mestranol 0.05mg)

- new low dose of time-proved ingredients
- established norethindrone/mestranol ratio
- lower patient cost

An uncommon steroid for common inflammatory dermatoses

In everyday topical steroid therapy, Synalar produces rapid resolution of inflammation and itching in steroid-responsive dermatoses—and at relatively low cost to the patient.

Advanced molecular design enhances potency

Synalar combines the advantage of earlier corticosteroid compounds with unique structural innovations. As a result, preparations of Synalar 0.01% and Synalar 0.025% have been reported to be more potent topically and significantly more effective than hydrocortisone 1.0%. The unique fluocinolone acetonide molecule provides one of the most useful topical corticosteroids for everyday practice.

Impressive clinical results in a wide range of dermatologic problems

The clinical efficacy of Synalar has been extensively documented in the world literature. Commonly encountered diseases such as allergic and contact dermatitis, eczematous and seborrheic dermatitis, and neurodermatitis respond rapidly to Synalar, often where previous therapy with other topical corticosteroids has failed.

Low patient cost for wider usefulness

With Synalar, a high degree of efficacy does not mean high price. And—a small quantity goes a long way. Thus, your patients can often obtain the "economy" of a hydrocortisone preparation with the proved efficacy of a potent, truly advanced steroid.

Synalar®
fluocinolone acetonide





For everyday topical steroid therapy

Synalar® 0.01%

fluocinolone acetonide provides economy in two practical dosage forms

For general use, the most economical and widely applicable concentration of Synalar is 0.01% Cream in a water-washable, vanishing cream base. Synalar Solution 0.01% is especially valuable in dermatoses involving moist, intertriginous areas or hairy sites where creams and ointments do not spread or penetrate readily. Synalar Solution is a unique dosage form—clear, nongreasy, cosmetically elegant.

Product Information

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. *Precautions:* Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. *Side Effects:* Side effects are uncommon with topical corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. In such cases the agent should be discontinued and appropriate measures taken. *Availability:* Synalar (fluocinolone acetonide) Cream 0.025%—5, 15 and 60 Gm. tubes and 425 Gm. jars. Cream 0.01%—15, 45 and 60 Gm. tubes and 120 Gm. jars. Solution 0.01%—20 and 60 cc. plastic squeeze bottles. Ointment 0.025%—15 and 60 Gm. tubes. Neo-Synalar® (neomycin sulfate 0.5% [0.35% neomycin base], fluocinolone acetonide 0.025%) Cream—5, 15 and 60 Gm. tubes.

fluocinolone acetonide—an original steroid from

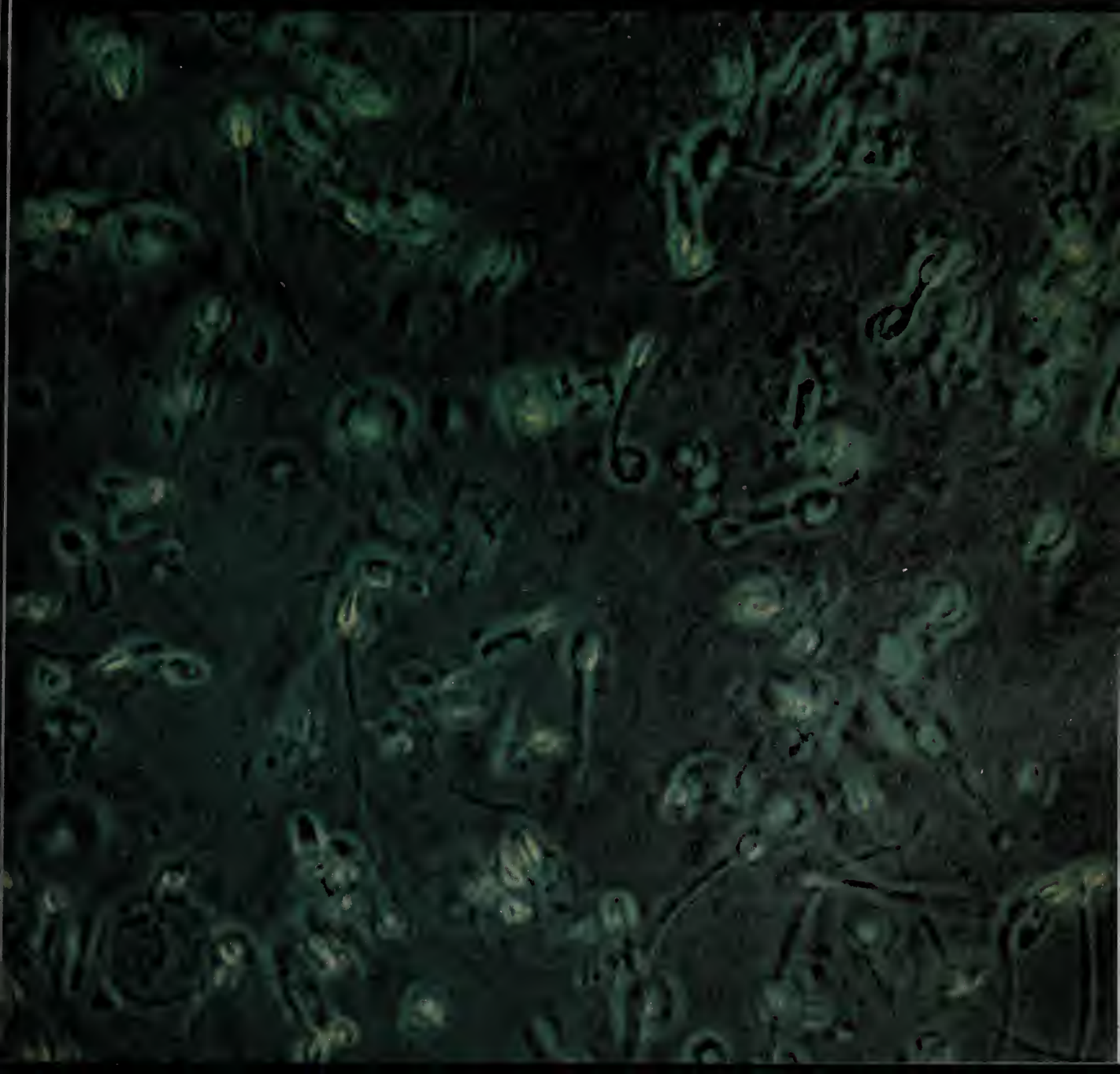
SYNTEX LABORATORIES INC., PALO ALTO, CALIF.



When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Prescribing Information

Contraindications: Patients with any symptoms or history of thrombophlebitis, pulmonary embolism, liver dysfunction or disease, carcinoma of breast or genital organs, or undiagnosed vaginal bleeding.

Warnings: Discontinue medication pending examination if there is sudden partial or complete loss of vision, proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. The safety of Norinyl-1 in pregnancy has not been demonstrated. If a patient misses two consecutive periods, pregnancy should be ruled out before continuing the medication. If she has not adhered to the prescribed schedule, pregnancy should be considered at the first missed period. Active ingredients of oral contraceptives have been detected in the milk of mothers who received these drugs; the significance to infants has not been determined.

Precautions: Pretreatment physical should include examination of the breasts and pelvic organs, as well as a Papanicolaou smear. If endocrine or liver function tests are abnormal during therapy, repeat tests are recommended after the drug has been withdrawn for two months. Following administration of drug, preexisting uterine fibromyomata may increase in size. Careful observation and caution are required for patients with symptoms or history of epilepsy, migraine, asthma, cardiac or renal dysfunction, cerebrovascular accident, psychic depression, and diabetes. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. Possible long-term effects of the drug on pituitary, ovarian, adrenal, hepatic or uterine function must await further studies. The physician should be alert to the earliest manifestations of thrombophlebitis and pulmonary embolism. The drug should be used judiciously in those young patients in whom bone growth is not complete. The age of the patient constitutes no absolute limiting factor, although treatment with Norinyl-1 may mask symptoms of the climacteric. The pathologist should be advised of Norinyl-1 therapy when relevant specimens are submitted.

Side Effects: The following have been observed with varying inciden in patients receiving oral contracep tives: nausea, vomiting, gastrointe tinal symptoms, breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edem chloasma or melasma, breast chang (tenderness, enlargement and secretion), change in weight (increa or decrease), changes in cervical erosion and cervical secretions, suppression of lactation when give immediately postpartum, cholestati jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression. Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation posttreatment, premenstruallike syndrome, changes in libido, changes in appetite, cystitislike syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, an itching. The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has neither been established nor disproved): thrombophlebitis, pulmonary embolism, neuroocular lesions.

The following laboratory tests may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic functior tests, coagulation tests (increase in prothrombin, factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from

SYNTEX

LABORATORIES INC., PALO ALTO, CALIF.



"Yes, Doctor, the pain is gone."

'EMPIRIN'® COMPOUND with CODEINE PHOSPHATE gr. 1/2 No. 3

Each tablet contains: Codeine Phosphate gr. ½ (Warning—May be habit forming), Phenacetin gr. 2½, Aspirin gr. 3½, Caffeine gr. ½.

■ Despite introduction of synthetic substitutes, efficacy of 'Empirin' Compound with Codeine remains unchallenged.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

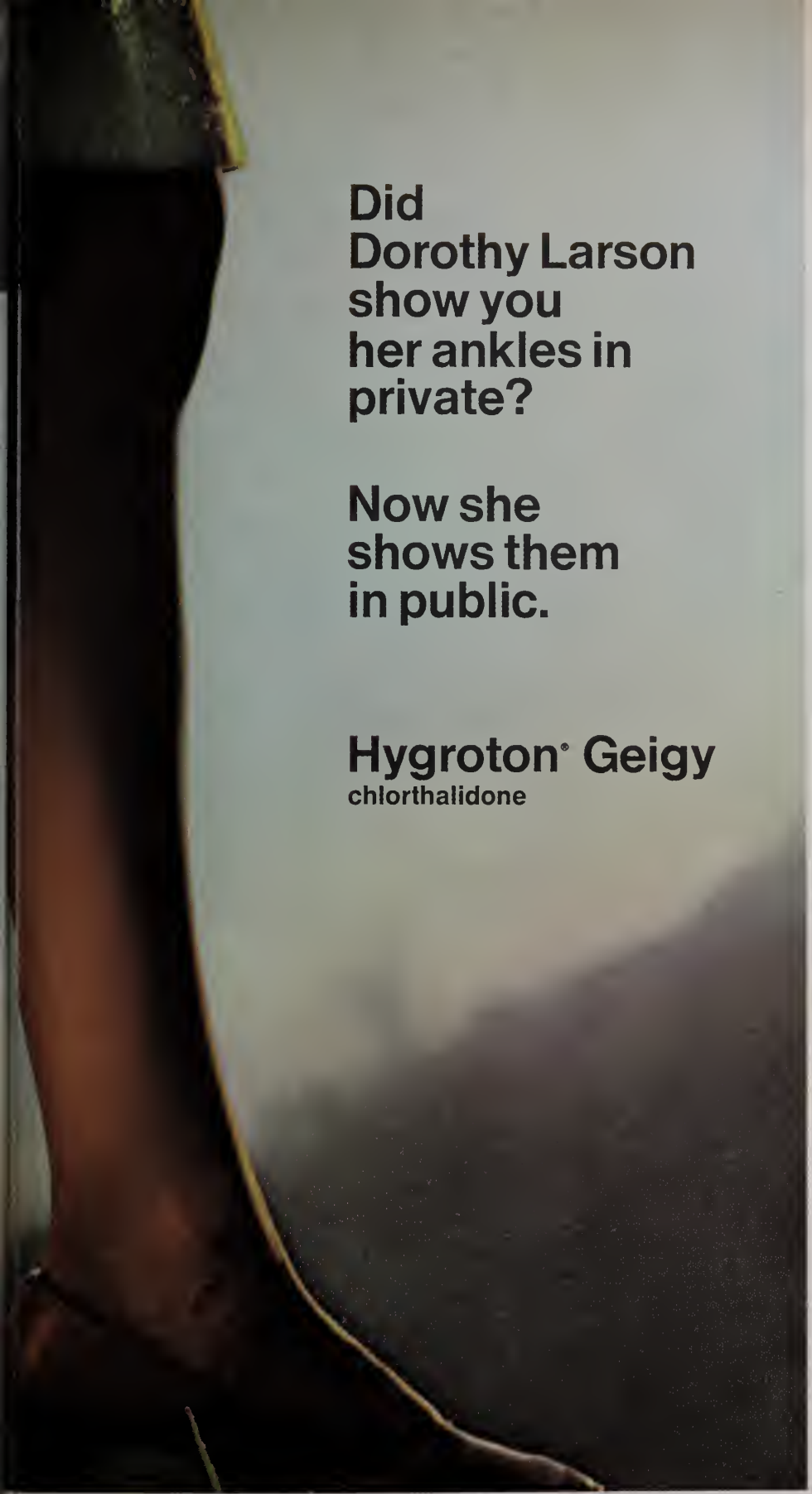


Indications: Hypertension and many types of edema involving retention of salt and water.
Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.
Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possi-

foration) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reac-

mia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Hygroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihyper-

may potentiate hypotension. Be
cause of the possibility of progr
sion of renal damage, periodic
determination of the BUN is ind
cated. Discontinue if the BUN ri
or liver dysfunction is aggravat
Hepatic coma may be precipita
Electrolyte imbalance, sodium
or potassium depletion may oc
If potassium depletion should o
cur during therapy, Hygroton sh



Did Dorothy Larson show you her ankles in private?

Now she shows them in public.

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vere ischemic heart disease and
patients receiving corticoste-
ds, ACTH, or digitalis. Salt re-
iction is not recommended.
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itation, vomiting, anorexia, con-
pation and cramping, dizziness,
akness, restlessness, hyperglyc-
mia, hyperuricemia, headache,

tension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

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Geigy

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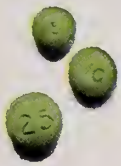
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(chlordiazepoxide)

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

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Anuncios y Suscripciones:
El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

Reimpresos:
Podrán ordenarse reimpresos de los artículos a publicarse cuando se reciba notificación de su aceptación.

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For details, see complete Prescribing Information.

Geigy Pharmaceuticals, Division of
Geigy Chemical Corporation, Ardsley, N.Y.

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in moderate hypertension and poorly controlled mild hypertension

(when diuretics or sedatives are inadequate, for example)



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When you consider using a drug *like* a broad-spectrum antibiotic, why not use a *true* broad-spectrum antibiotic? Like DECLOMYCIN.

References: 1. A.M.A. Council on Drugs: *New Drugs* 1966 ed. Chicago: American Medical Association, p. 12. 2. Osol, A.; Pratt, R., and Altschule, M.D.: *The United States Dispensatory*, 26th ed. Philadelphia: J. B. Lippincott Co., 1967, p. 844. 3. Purcell, R. H., and Chanock, R. M.: Role of Mycoplasmas in Human Respiratory Disease. *Med. Clin. N. Amer.* 51:791 (May) 1967.

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DEMETHYLCHLORTETRACYCLINE

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Prescribing information on next page.

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DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines when the offending organisms are tetracycline-sensitive.

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Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth — dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; **Tablets:** film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

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LEDERLE LABORATORIES, A Division of American Cyanamid Company, Pearl River, New York

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DS4 5/67 & DS7 5/67 COMBINED

4537—

BAGASSOSIS
Allergic and Immunological Aspects

O. Bonilla Soto, PhD, MD

Bagassosis is a disease of the respiratory system secondary to the inhalation of bagasse dust. Bagasse is the name given to the fibrous material which remains after the sugar cane is crushed and the sugar containing juice is expressed. Formerly this material was discarded but now it is being used for the manufacture of insulating and acoustic boards, paper, fertilizer, poultry feed, explosives and brick. Usually it is baled and if not used immediately may remain exposed in the field for long periods. Workers employed in handling and breaking these bales disperse and inhale dust particles and develop symptoms of a respiratory illness.

The etiology and specific physiopathological mechanisms involved in this disease remain unknown but the close relationship between the patient's work and the characteristic clinical picture point clearly to a cause and effect relationship between exposure to bagasse dust and the development of the symptoms.

From the Department of Microbiology of the School of Medicine of the University of Puerto Rico, San Juan, Puerto Rico.

Presented at the 64th Annual Meeting of the Puerto Rico Medical Association, November 17, 1966, San Juan, Puerto Rico.

Methods and Results

This work was performed to evaluate the role of possible allergic and immunologic mechanisms in the etiology of the disease. A bale of bagasse was obtained from a paper mill in which over 50 cases of bagassosis have been reported.

One gram of bagasse dust was shaken with 50 ml of sterile isotonic saline and various dilutions were prepared and inoculated on plates of Merhlich's medium. The plates were incubated at room temperature for 5 days and the mold colonies counted. A total of 21,000,000 molds spores per gram of bagasse were found. *Aspergillus* and *Penicillium* colonies were present in approximately the same numbers and constituted about two thirds of the colonies. *Mucor* and *Phoma* made up the remainder.

Loopfuls of the bagasse suspension were inoculated in trypticase soy agar. Abundant bacterial growth was obtained consisting chiefly of gram negative bacilli and yeasts. *Aerobacter cloacae* was identified. Non-lactose fermenting, gram negative bacilli were also present.

Twenty guinea pigs were exposed to the inhalation of bagasse dust in a specially constructed plastic chamber. One hour long daily exposures were performed on sixteen consecutive days. Three of the animals died after 12 hours of exposure. The rest of the animals as well as 5 non-exposed controls were sacrificed and sections of the lungs prepared for pathological studies.

Figure 1 is representative of the appearance of the guinea pig lung after 12 hours exposure to bagasse dust. Considerable thickening of the alveolar septae was evident. The thickening was due to increased mononuclear infiltration, histiocytes and dilation of the capillaries. The thickening

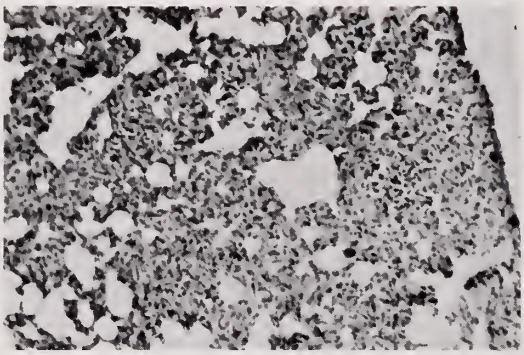


Fig. 1: Thickening of the alveolar septae in guinea pig lungs after 12 hours exposure to bagasse dust.

caused collapse of the alveoli or diminution in their size. Compensatory emphysema was also present in many areas.

Figure 2 shows the appearance of the thickened areas under higher magnification. Notice the

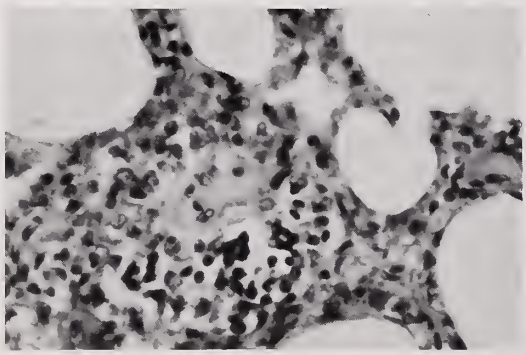


Fig. 2: Thickened area under higher magnification showing mononuclear infiltration, histiocytes and dilatation of the capillaries.

typical nodular type of mononuclear infiltration consisting chiefly of lymphocytes, monocytes and histiocytes throughout the entire lung parenchyma.

Figure 3 demonstrates nodule formation which in some areas appeared as definite lymphoid follicles.

Figure 4 shows another section of the lung in which there was marked eosinophilic infiltration and an occasional giant cell.

A 10 per cent bagasse extract was prepared in Coca's extracting fluid using defatted bagasse

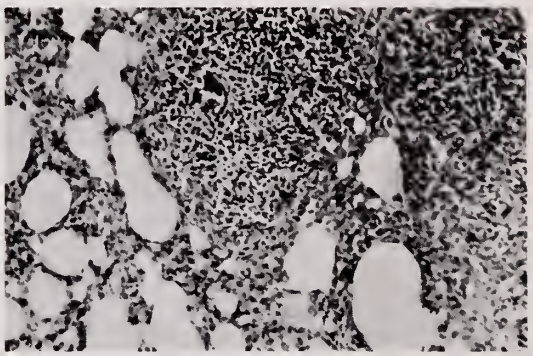


Fig. 3: Nodular type of mononuclear infiltration taking the form of definite lymphoid follicles.

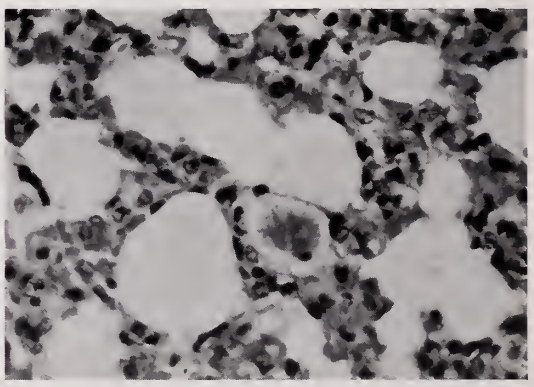


Fig. 4: Section of lung parenchyma showing eosinophilic infiltration and occasional giant cells.

powder. Rabbits were immunized by intradermal injections of the bagasse extract emulsified with complete Freund's adjuvant.

Gel-diffusion studies were carried out with the rabbit anti-bagasse serum using as antigen a concentrated bagasse extract. Three bands of precipitation were obtained. The sera failed to precipitate with extracts from the molds contaminating the bagasse.

Serum was obtained from 29 individuals who had suffered from bagassosis. Most cases had recovered, but a few had residual symptomatology. These sera were studied by gel diffusion against concentrated bagasse extract. Ten normal human sera were similarly tested. Nineteen out of the 29 patients' sera gave one band of precipitation. The control sera were negative. These patients were also skin tested with a 1:100 dilution of a 10%

TABLE I: ARTHUS REACTIONS IN RABBITS IMMUNIZED WITH BAGASSE

Rabbit	Fr.*9	Fr. 20	Fr. 33	Fr. 36	Fr. 58	BE***	Buffer
1	20**	20	20	20	0	21	0
2	20	20	20	20	0	18	0
3	20	15	15	20	0	20	0
Normal Rabbit	0	0	5	0	0	0	0

*Fr.—Sephadex fractions.
**Ave. diameter zone of edema 4 hours after the intradermal injection.
***BE—Bagasse extract.

bagasse extract, and with a 1:1000 dilution of extracts from 4 molds isolated from bagasse. Fifty two per cent gave positive intradermal immediate reactions to bagasse. One of 10 normal individuals reacted to the extract. None of the patients reacted to the mold extracts. There was no close correlation between the precipitation and the intradermal tests.

Attempts were made to fractionate the components of the bagasse extract by gel filtration in Sephadex G-200. Fractions were collected and read in a Beckman DU spectrophotometer at 220 and 280 mμ. The fractions were studied also by gel diffusion using rabbit anti-bagasse serum. The results are shown in Figure 5. Three peaks were obtained at 220 mμ as indicated by the solid line.

The first peak gave one band of precipitation with immune serum. The second peak gave 3 prominent precipitation bands. The largest peak, which coincided with the single peak obtained at 280 mμ and is shown by the broken line, gave no precipitation. Pools of fractions comprising peaks 2 and 3 gave positive intradermal tests in cases of bagassosis but a few reacted also to a pool from fractions 70-74. None reacted to the buffer alone.

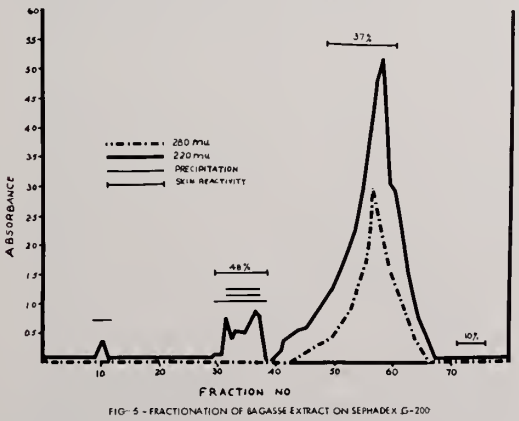


FIG. 5 - FRACTIONATION OF BAGASSE EXTRACT ON SEPHADEX G-200

Fig. 5: Fractionation of bagasse extract on Sephadex G-200.

Intradermal tests were performed in immunized rabbits using 0.1 ml of 10% bagasse extract and Sephadex fractions representing peaks 1, 2 and 3 respectively. Fractions 20 and 58 were selected as representatives of zones of zero reading. The same material was injected into a normal rabbit as control. The results shown in table I give the average diameter of the areas of edema at the injected sites 4 hours after injection. Whole bagasse extract as well as fractions from peaks 1 and 2 which represents the zones containing precipitating antigens gave positive Arthus reactions. Fraction 58 representative of the third peak which failed to precipitate with anti-bagasse serum, gave a negative Arthus reaction. Fraction 20, representing a zone of zero reading gave a positive reaction, suggesting possible contamination with antigenic material. Negative reactions were obtained in all cases in the normal rabbit.

Discussion

Many cases of bagassosis have occurred in Puerto Rico (1) and in other countries engaged in industries derived from the sugar cane. The clinical and pathological studies which have been carried out have failed to establish the etiology of the disease.

Some investigators have postulated the

possibility that the disease may result from an allergic sensitization to components of bagasse or to microorganisms contaminating the inhaled particles (2). Others deny the allergic hypothesis and believe that it is due to the irritation produced by some chemical or physical property of the dust or its microbial flora (3).

A few investigators have made an experimental approach to the problem of the etiology of bagassosis. Smetana and co-workers (4) introduced native bagasse powder into the respiratory passages of guinea pigs, cats, rabbits and monkeys and obtained a reactive process which was mainly interstitial and characterized by septal monocytic cells, edema and congestion of the pulmonary vessels and thickening of the alveolar septa. Evidence of hypersensitivity to a protein antigen of bagasse could not be elicited and precipitin antibodies to bagasse protein did not develop in rabbits. There was however, a sensitivity to the crude extract of bagasse as demonstrated by skin tests of workers and in experimental animals exposed to bagasse dust.

Gerstl and co-workers (5, 6) similarly exposed rabbits and guinea pigs to bagasse dust and reported striking differences between lesions resulting from the administration of live bagasse and those from bagasse dust with all living matter killed by either autoclaving or formalizing. The bagasse fiber, without living matter, elicited long-standing foreign body reactions. Bagasse dust in the native state, when inhaled or insufflated, called forth, in addition to the foreign body granuloma, an acute inflammatory response which suggested that a self-propagating microorganism was acting upon the tissue of the host.

We believe that our success in getting an antibody response in rabbits, which other investigators had failed to accomplish, is probably due to our use of adjuvants for the immunization and greater concentration of the immunizing material.

The lack of correlation between precipitation and skin tests in these patients suggests that exposure to bagasse dust induces in patients different types of antibodies. One of them seems to be the skin sensitizing, non-precipitating reaginic type of antibody, which is thought to be responsible for the immediate type of sensitivity. Another one appears to be the precipitating type of antibody which does not fix to the human skin. The role played by these antibodies in the pathologic process in the lungs remains to be investigated.

Summary

It has been shown that the inhalation of bagasse dust produces in the lungs of guinea pigs, pathological changes characterized by a prominent interstitial mononuclear infiltration. The bagasse dust was highly contaminated with molds, specially *Aspergillus* and *Penicillium* as well as with *Aerobacter cloacae* and other gram negative bacilli.

Extracts of the soluble components of bagasse were antigenic in rabbits. The failure of mold extracts to precipitate with the immune serum suggests that the antibodies were probably elicited by components of the bagasse fibers per se and not by the contaminating molds.

The serum from two thirds of the individuals who had suffered from bagassosis gave a faint precipitation band against bagasse extract. Fifty two per cent of the individuals

gave positive immediate skin reactions to bagasse and none reacted to the mold extracts.

Fractionation of the bagasse extract in Sephadex G-200 revealed 3 components. The antigenic material as revealed by precipitation, was found only in the first 2 components, but the third component while failing to precipitate, gave positive intradermal reaction in patients.

The role played by these antibodies in the pathologic process in the lungs remains to be investigated.

Resumen

Se ha demostrado que la inhalación de polvo de bagazo produce en los cobayos cambios patológicos caracterizados por una marcada infiltración mononuclear de tipo intersticial. Se encontró que el polvo de bagazo estaba altamente contaminado con hongos, especialmente *Aspergillus* y *Penicillium,* así como también con *Aerobacter cloacae* y otros bacilos gram negativos.

Extractos de los componentes solubles del bagazo demostraron ser antigénicos en conejos. Extractos de los hongos aislados del bagazo no precipitaron con el suero inmune, lo que sugiere que los anticuerpos probablemente son inducidos por componentes de la fibra del bagazo en sí y no por los hongos contaminantes.

El suero de dos terceras partes de los individuos que habían padecido de bagasosis dió una tenue banda de precipitación contra el extracto de bagazo. El 52 por ciento de estos pacientes dió una cutirreacción positiva al extracto de bagazo y ninguno reaccionó a los extractos de hongos.

Se obtuvieron tres componentes al fraccionar el extracto de bagazo en Sephadex G-200. El material antigénico, demostrado por la técnica de precipitación, se encontró solamente en los primeros dos componentes, pero el tercer componente, aunque incapaz de precipitar, dió no obstante una cutirreacción positiva en los pacientes.

Se obtuvieron reacciones de Arthus positivas en conejos inmunizados al provocarse la reacción inyectando extractos de bagazo crudo o las fracciones precipitantes obtenidas de la columna de Sephadex.

Se concluye que, la fibra de bagazo en sí, contiene componentes antigénicos capaces de inducir reacciones alérgicas en animales sensibilizados y en pacientes con bagasosis. Esto no elimina la posibilidad de que la flora microbiana o las propiedades irritantes de la fibra del bagazo tomen parte en el proceso patológico.

Acknowledgement

The author is indebted to Dr. Rafael Ramírez Weiser from the Department of Pathology, School of Medicine, for the pathologic studies and to Drs. Arnaldo Roldán and Ernesto González from the Department of Health for their kind help in obtaining the patients and pathologic material required for this study.

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LEPROSY IN PUERTO RICO
A new Look at an Old Disease

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Definite information regarding the date and manner of introduction of leprosy into Puerto Rico is lacking. Doull et al (1) state that it is generally believed to have been imported from Africa in the early days of the slave trade. It appears that by the last quarter of the eighteenth century the disease was generalized in the island, for Fray Iñigo Abbad, writing in 1788, says:

"Mal de San Lázaro, o sea la elefantiasis de los griegos, ha desaparecido de los pueblos de Europa situados entre los 40º y 55º de latitud; los casos que allí se observan son importados de los demás puntos del globo. Deseamos a Puerto Rico igual beneficio: pero por ahora nos es doloroso hacer constar que es enfermedad muy generalizada." (2)

Nothing was done to control the disease until 1870, when the Provincial Deputation recommended the construction of a leprosarium. The recommendation was not followed, however, and efforts to have each municipality take care of its own leprosy patients also failed. In 1880, San Juan built a "hospital" with accommodations for six patients in the rear of the jail.

Following the Spanish-American War, Military Governor Henry established a Board of Health for San Juan, and $100 of military funds were used to repair the hospital, which was declared an insular institution. In May 1899, search was made in San Juan for leprosy patients and 11 were segregated. By April 1900, there were 18 patients.

The following year, the hospital was moved to the former Quarantine Station, located on Isla de Cabras, just off the north coast of the island. On June 30, 1902, there were ten male and seven female patients confined. The number increased annually, until, in 1914, there were 39 patients. The number of patients remained fairly constant for the next twelve years. On June 29, 1926, 43 patients were transferred to the new Insular Leprosarium, in Barrio Cuevas, Trujillo Alto. During the years from 1926 to 1941 the patient load fluctuated from 50 to 60. On June 30, 1940, the census was 45 (1).

Currently, on December 1, 1966, there are 24 patients in the hospital and colony at Trujillo Alto.

Material and Methods

Short of undertaking a long-term, large-scale, almost house-to-house survey, it is obviously impossible to arrive at an exact quantitative statement of the prevalence of Hansen's disease in Puerto Rico. The data presented in this paper

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have been gathered from the following sources.

1. The records of the Insular Leprosarium at Trujillo Alto, P.R. Three hundred four patients have been admitted to this institution. Of these, 162 are dead; 142 survive. An attemp has been made to locate and interview as many as possible of the patients, past and present; to learn the names and whereabouts of all members of the extended family of each; and to interview each.

2. The records of the Division of Preventive Medicine and Communicable Disease, of the Commonwealth Department of Health. Patients contained on the list of cases of leprosy reported since 1940 number 200. Of these, 63 are duplicated on the Leprosarium list: 137 are non-duplicated cases. The living among the latter; together with members of their families, have been investigated in the same manner as patients in the first category.

3. The records of the United States Leprosarium, at Carville, La., insofar as they pertain to patients of Puerto Rican provenance. Sixty-seven cases were reported, of which 32 were duplicated on other records. The same method of investigation as in the first two categories was followed for patients still residing in Puerto Rico.

4. The records of the New York City Health Department, Bureau of Preventable Disease, dating back to 1948, as regards migrants from Puerto Rico. Twenty cases were reported, of which three were duplicates.

5. All members of the Section of Dermatology of the Puerto Rico Medical Association have been personally requested by the president of the organization to contribute, confidentially, information concerning patients, past or present, whom they have treated for leprosy. Thirty-five new cases were reported.

6. All five District Hospitals in Puerto Rico have given access to their records. Only one new case was found.

7. Municipal hospitals and health centers in 35 towns of Puerto Rico have been visited and their records searched for cases of leprosy.

8. Seventeen physicians in private practice — general practitioners. pathologists, and others, have been interviewed with regard to patients treated.

The limitations of these avenues of approach are obvious. They may be described, in part, as follows:

1. Migrants from Puerto Rico live in many other parts of the United States besides New York. Large colonies exist in Chicago, Connecticut, Ohio and New Jersey. Within the time limitations of this study it has been impossible to investigate the records of each town and city on the continent with a Puerto Rican population.

2. Some dermatologists have been reluctant to reveal privileged information concerning their patients.

3. It has been impossible to approach every general practitioner on the island, some of whom may be treating cases of leprosy. The diagnosis of the disease is far from obvious: many physicians report never having seen a case. It is entirely possible that cases are being treated, in whom the diagnosis has not been established.

4. Some patients who have become aware, by one means or another, of their diagnosis hide the fact that they have leprosy.

In view of these limitations, it must be recognized that the number of cases of leprosy reported is a minimum and may fall far short of the true number.

Results

Prevalence

The cases of leprosy located and the sources from which information was obtained are summarized in Table I.

It can be said, then, that there are a minimum of 275 cases of leprosy among surviving Puerto Ricans—i.e., persons born in Puerto Rico. Of these, 219 are living on the island; 24 are at Carville; 20 are living in New York; nine are in the United States in places other than New York; and three are living in the Lesser Antilles.

It must be emphasized that the figure 275 represents a minimum. Most dermatologists believe that for every known case of leprosy there exist four or even five others which have not been reported (3). If one

TABLE I: SOURCES FROM WHICH INFORMATION ON CASES OF LEPROSSY WAS OBTAINED

Source of Information*	Living	Dead
Insular Leprosarium, Trujillo Alto	142	162
Division of Preventive Medicine, Commonwealth Department of Health	45	92
U.S. Leprosarium, Carville, La.	32	
City of New York Department of Health	17	
Dermatologists in Puerto Rico	35	
District hospitals	1	
Other hospitals	0	
Private physicians	3	
Totals	275	254

* December 1, 1966. Only induplicated cases are included.

accepts this estimate, the probable number of cases of leprosy among Puerto Ricans lies between 1,100 and 1,375.

Of the 275 known cases among Puerto Ricans, 219 are living in Puerto Rico and 10 more are temporarily at Carville. According to the Bureau of Demographic Registry, Department of Health, Commonwealth of Puerto Rico (4), the estimated population of Puerto Rico in 1965 was 2,625,000. Accordingly, the total cases of Puerto Rican residents with leprosy represents 8.7 per 100,000 inhabitants of the island.

Incidence

Leprosy is, by law, a reportable disease in Puerto Rico. Table II lists the new cases reported, by year, since 1940, to the Bureau of Control of Communicable Diseases,

TABLE II: INCIDENCE OF LEPROSY IN PUERTO RICO 1940 - 1964

Year		Cases Reported
1940	(21) *	12
1941		7
1942		11
1943	(35) *	8
1944		**
1945	(12) *	10
1946		6
1947		10
1948		6
1949		5
1950		2
1951	(13) *	9
1952		14
1953		12
1954		16
1955		1
1956		5
1957		2
1958		1
1959		**
1960		6
1961		2
1962		4
1963		7
1964		3

* Of the 21 cases reported for 1940, 9 are listed as from Barrio Cuevas, where the Leprosarium is located. It seems problable that these 9 cases were not newly diagnosed in 1940 but represent patients in the Leprosarium, whose names had not previously appeared in the incidence record. Similar situations occur in 1943, when 35 cases are listed, but 27 are from the Leprosarium; in 1945, when, of 12 cases listed, 2 are from the institution; and in 1951, when of 13 cases listed, 4 are from the Leprosarium.

** The records for the years 1944 and 1959 are missing from the files.

Data from Bureau of Control of Communicable Diseases, Division of Preventive Medicine, Department of Health, Commonwealth of Puerto Rico.

Division of Preventive Medicine, of the Commonwealth Department of Health.

The number of new cases per year ranges from 1 to 16; the mean number of new cases per year, for the 23 years for which records exist, is 6.9.

Geographic Distribution

Addresses in Puerto Rico were ascertainable for 223 of the 275 known cases. The number of cases from each municipality and the rate per 100,000 is shown in Table III.

The number of cases and the rate per 100,000 for component parts of San Juan are shown in Table IV.

Three municipalities have rates greater than 40 per 100,000: Hormigueros, Naguabo and Vieques. The first two lie on the coast; Vieques is an island. Three other municipalities have rates over 30 per 100,000. Mayagüez and Vega Baja are situated on the coast. Trujillo Alto presents a special case because of the location there of the Insular Leprosarium.

Age at Onset

It was possible to determine approximate age at onset of the disease in 176 of our cases. Table V shows the number of cases diagnosed in each decade of life. The decades during which the greatest number of patients demonstrate the first symptoms are the teens and the twenties —the period of adolescense and of child-bearing— but a considerable number of cases appear in the two succeeding decades.

Family Relationships

During the course of this investigation,

TABLE III: NUMBER OF LEPROSY BY MUNICIPALITY, DECEMBER 1966

Municipality	No.	Rate per 100,000
Adjuntas	4	20.3
Aguada	1	4.3
Aguadilla	5	10.4
Arecibo	10	14.3
Barceloneta	1	5.2
Bayamón	4	5.5
Cabo Rojo	6	24.1
Caguas	4	6.1
Carolina	2	4.9
Cataño	1	4.0
Cayey	1	2.6
Ceiba	2	22.0
Ciales	2	11.0
Guánica	2	14.5
Guayama	1	3.0
Guayanilla	1	5.7
Hormigueros	3	41.9
Humacao	1	3.0
Isabela	1	3.5
Juncos	3	14.0
Lares	1	3.7
Luquillo	2	23.3
Manatí	8	27.3
Maunabo	3	27.8
Mayaguez	26	31.0
Morovis	4	22.1
Naguabo	17	98.9
Patillas	1	5.8
Ponce	15	10.3
Río Grande	2	11.6
San Germán	3	10.8
San Juan	41	9.1
San Lorenzo	1	3.6
San Sebastián	1	3.0
Toa Alta	1	6.4
Trujillo Alto	6	32.9
Utuado	1	2.5
Vega Alta	4	22.7
Vega Baja	10	33.1
Vieques	3	41.6
Yabucoa	1	3.4
Yauco	1	2.9

TABLE IV: NUMBER OF CASES AND RATE OF LEPROSY FOR COMPONENT PARTS OF SAN JUAN DECEMBER 1966

Section	No.	Rate per 100,000
Hato Rey	1	1.0
Río Piedras	14	13.7
Santurce	14	7.9

we interviewed 65 patients and 58 close relatives of patients. Complete listings of the families of each patient were made, including grandparents, parents, siblings, aunts and uncles, cousins, children and grandchildren, with special reference to the existence of leprosy in any other member of the family.

Twenty-five patients, or 20.3 per cent, were found to have relatives who suffer from the disease. The relationships are distributed as shown in Table VI. Strangely, in our group there was no case of a leprous mother.

We have three cases of married couples, where both spouses have the disease. One couple is childless; a second has three children under the age of seven, none of whom has shown symptoms. The third case, in which the husband is in New York, is said to have five out of six children suffering from the disease. But this has not been documented.

TABLE V: AGE AT ONSET OF LEPROSY

Age at onset	Number of patients
0 — 9	6
10 — 19	38
20 — 29	43
30 — 39	31
40 — 49	30
50 — 59	14
60 — 69	11
70 — 79	3
Total	176

TABLE VI: RELATIVES OF LEPROSY PATIENTS ALSO INFECTED

Relationship	No.
Grandparent	2
Father	9
Son or daughter	5
Sibling	15
Aunt or uncle	2
Cousin	3
Nephew or niece	1

Race and Economic Status

In Puerto Rico, where skin color runs the entire gamut from pure white to pure black and where siblings often differ widely in the degree to which they possess negroid characteristics, it is often difficult to classify a given individual as white, mulatto or negro. Of the 123 individuals interviewed for this study, 97, or 79 per cent, were classified as non-white. As this percentage is somewhat higher than that for the population as a whole, in our group there appears to be a slight tendency for colored people to be more susceptible to leprosy than are whites.

Leprosy is, *par excellence,* a disease of the poor. In our group of 123, only five individuals, or four per cent, belong to the middle class; all the rest belong to the socio-economically lower class. Since colored people are over-represented in this social class, the racial difference may by wholly explicable on economic grounds.

Discussion

Two earlier studies have been made of leprosy in Puerto Rico. Palacios (5), writing in 1929, reported 137 cases. Approximately 100 were duly inscribed in official records; the remaining 40 were found by the investigator.

Writing in 1941, Doull et al (1) reported collecting the names of 83 living persons in Puerto Rico suffering from leprosy. This they did by enlisting the aid of all health officers, who were asked to submit, from memory, the names of all cases of leprosy seen at their respective health units. A fire had destroyed the records of the Department of Health in 1937, and the only records which remained were of patients who had been admitted to the Leprosarium and those of deceased persons on whose death certificate leprosy was listed as a cause of death. He supplements this figure by resort to the arithmetic calculation shown in Table VII.

Accepting the amended figure of 102 as the number known cases on the island in 1940, it appears that the absolute number of known cases has been multiplied by a factor of 2.7, to 275, in the past 26 years. In 1940, the population of Puerto Rico was 1,869,255 (6); the rate per 100,000 inhabitants was 5.5 in that year. The current rate of 8.7 per 100,000 represents an increase of 59% in the intervening quarter century.

TABLE VII: CALCULATION BY DOULL (1) OF CASES OF LEPROSY IN 1940

Remaining in Leprosarium, Dec. 31, 1931	58	
New cases reported, Jan. 1, 1932 to Dec. 31, 1939	102	160
Registered deaths, Jan. 1, 1932 to Dec. 31, 1939		58
Alive on Dec. 31, 1939		102

How much of this discrepancy represents a real increase in prevalence and how much is attributable to the greater number of physicians now practicing, better methods of case-finding and greater accuracy in reporting is open to question.

As regards incidence, Doull et al (1) list the cases reported for the years 1928-1939, inclusive. The range for these 12 years is from 4 to 22; the mean is 10.9. In their case, as in ours, (*vide supra,* Table II) it is probable that the cases from Trujillo Alto are overstated because of periodic listing of cases in the Leprosarium which do not previously appear in the record.

It is interesting to note that, while prevalence, as given by him, is only three-eights that found in the present study, incidence is two-thirds higher. This may be a reflection of the increased longevity of leprosy patients with administration of the newer sulfone therapy and of increased longevity, in general, in Puerto Rico.

Palacios, in 1928, (5) speaks of the "apparent immunity to leprosy on the part of the interior hill country." Doull et al, in 1941 (1), note that the municipalities of Naguabo, Patillas and Vega Baja, with a combined population of only 3.4 per cent of that of the island, were recorded as places of birth of 32.6 per cent of the death certificates mentioning leprosy, roughly ten times the number expected if geographic distribution were uniform. Further, Aguadilla, Arecibo and Mayaguez, with a combined population of about 10 per cent of

the total, contributed approximately 20 per cent of the cases reported over the 12-year period 1928-1939. It will be noted that all six municipalities mentioned lie on the coast.

In the present study, Naguabo, with a rate of 98.9 per 100,000, continues to lead all other municipalities by a wide margin. Palacios (5) found the rate in 1927 to be 120. Vega Baja, with 33.1 (compared to Palacios' finding of 68.0) and Mayaguez, with 31.0, continue to be among the municipalities with high prevalence. On the other hand, Patillas has fallen to 5.8, actually below the rate for the whole island, and Aguadilla, with 10.4, and Arecibo, with 14.3, exceed the general rate only moderately.

Table VIII shows a comparison of the prevalence rates found in certain municipalities by Palacios in 1928, by Doull in 1940, and by ourselves in 1966.

Several considerations present themselves as possible contributory factors in the higher prevalence of leprosy on the coast. First, leprosy, may have been introduced into Puerto Rico by negro slaves from Africa. It continues to have a higher prevalence among Negroes than among whites *(vide supra,)*. But the slaves were used almost exclusively in the cultivation of sugar on the coastal plain. To this day Negroes constitute a much smaller fraction of the population in the mountains of the interior than on the coast.

Secondly, while leprosy spares no social class, it is especially prevalent among the lower socio-economic groups. On the coast, and especially in the cities, people of this class tend to live crowded together in slums. In the country, on the other hand, while individual houses may be quite as poor and quite as densely occupied as in the cities, they are usually separated from each other by distances ranging from 100 yards to a quarter mile.

TABLE VIII: PREVALENCE OF LEPROSY IN SIX MUNICIPALITIES OF PUERTO RICO IN 1927, 1940 AND 1966. RATE PER 100,000

Municipality	Prevalence in 1927 (%)	in 1940 (1)	in 1966
Aguadilla	7.0)		10.4
Arecibo	12.0)	11.5*	14.3
Mayagüez	11.0)		31.0
Naguabo	120.0)		98.9
Patillas	98.0)	54.7*	5.8
Vega Baja	68.0)		33.1

* Doull et al do not give figures for the municipalities individually. They state only that "Aguadilla, Arecibo and Mayagüez, the combined population of which was about 10 per cent of the total population of the Island in 1930, contributed approximately 20 per cent of the total cases notified in the twelve year period," and "The municipalities of Naguabo, Patillas and Vega Baja, with a combined population of only 3.4 per cent of that of the Island, were recorded as places of birth on 32.6 per cent of the certificates, or on about ten times as many as would be expected."

The fact that in our group there appears a slight tendency for colored people to be more susceptible to leprosy than whites must be viewed with caution. Badger (9) points out that in Louisiana, the State which has had the greatest number of cases of leprosy, the rate per thousand for whites has been nearly three times that for Negroes and that the variations of incidence

among various racial groups is due to contact rather than to racial susceptibility.

The existence of well-defined foci in Puerto Rico is not surprising. Simons (8) states:

> *"It is interesting to note that, in each country a certain region, in each region a certain district, in each district a certain street, and in each street a particular part forms a more intensive focus within another focus: the* endo-epidemic."

The mode of transmission of leprosy is not known, but it appears to be favored in situations where people live in close association. Fairly prolonged contact with a leprosy patient is a necessary condition for infection (7).

Age at onset of the disease is extremely difficult to determine. It is believed by many leprologists that infection always occurs in childhood. But the early signs and symptoms are often so insignificant and so transitory that they are overlooked. Typically, the disease then enters a long dormant period, lasting from five to 30 years and appears overtly at a time when the patient is subject to unusual physiological stress. Adolescence, pregnancy in women, intercurrent disease with high fever are periods at which leprosy is likely to manifest itself.

The consistently large fraction of families in which more than one case exists is explained on the basis of infection of one member by another or by a common source. This is, in all likelihood, the correct explanation. Yet, the possibility that differences in antibody formation and hence in susceptibility may be carried by the genes cannot be ruled out in the present state of knowledge.

Summary

A study of the incidence of leprosy among Puerto Ricans is reported. The study includes review of all available records plus field visits.

There exists a minimum of 275 documented cases of leprosy among Puerto Ricans. Two hundred nineteen are currently on the island; 53 in the United States; three elsewhere. It appears probable that the total number of cases lies between 1,100 and 1,400.

Over the past quarter century the reported incidence of new cases has ranged from one to 16 per year, with a mean of 6.9.

The rate for the entire island is 8.7 cases of leprosy per 100,000 inhabitants. The majority of the patients inhabit the coastal areas with Naguabo leading all municipalities in concentration of cases.

Onset signs and symptoms of leprosy may occur in every decade of life. The modal decades are the teens and twenties.

Multiple cases of leprosy were found in 20.3 per cent of the families interviewed.

Non-whites and the lower socio-economic classes suffer disproportionately from the disease. The two facts are probably related.

Resumen

Se presenta un estudio sobre la incidencia de la lepra en los puertorriqueños. El estudio incluye una revista de todos los records disponibles, más visitas de campo.

Existen por lo menos 275 casos documentados de lepra en puertorriqueños. Doscientos diecinueve residen actualmente en la isla; 53 en los Estados Unidos; tres en otras partes. Se supone que el total de casos sea entre 1,100 y 1,400.

Durante el pasado cuarto de siglo la incidencia informada de casos nuevos ha fluctuado entre uno y 16 por año. El promedio ha sido 6.9.

La tasa para la isla entera es de 8.7 casos de lepra por 100,000 habitantes. La mayoría de los pacientes provienen de las áreas costaneras con Naguabo manteniéndose al frente de los demás municipios en concentración de casos.

El comienzo de la lepra puede ocurrir en cualquier década de la vida. Las décadas en que aparecen más casos son la segunda y la tercera.

Existen casos múltiples de lepra en un 20.3 por ciento de las familias entrevistadas.

Los no blancos y las clases socio-económicas bajas padecen desproporcionalmente de la enfermedad. Los dos hechos están probablemente relacionados.

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CONSECUENCIAS DEL CAMBIO DEL METODO DURANTE UN EXPERIMENTO

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El 24 de noviembre de 1965 los pediatras del Curso Internacional de Pediatría Social, llevado a cabo en la Ciudad de Guatemala, fueron a la Casa del Niño para realizar ciertas medidas antropométricas de los niños. Consideraremos aquí los resultados de los pesos, tomados con tres balanzas diferentes, a los doce niños estudiados. Cuando solamente tres niños faltaban de ser pesados, se observó que la balanza número 3 registraba valores de aproximadamente ocho libras de más y, por esta razón se decidió descontinuar el uso de esta balanza y usar solamente las números 1 y 2. El presente trabajo demuestra que el dejar de usar la balanza en error fue una gran equivocación, y que habría sido mucho mejor continuar usando la balanza número 3 para que los métodos estadísticos pudieran ser aplicados.

Introducción

Se realizaron en doce niños cinco observaciones del peso individual de manera que cada uno tuvo dos medidas con la balanza número 2; los niños del número 1 hasta el 9 tuvieron dos medidas realizadas con la balanza número 1 y una con la balanza número 3; los niños números 10, 11 y 12 tuvieron tres medidas con la balanza número 1 y ninguna con la balanza número 3. Los datos son reportados en la Tabla I.

Presentado al Curso Internacional de Pediatria Social auspiciado por el Instituto de Nutrición de Centro América y Panamá el 7 de diciembre de 1965, en Guatemala.

Modelo Matemático

Al examinar los datos de la Tabla I se ve fácilmente que la balanza número 2 siempre mide un poco más que la balanza número 1, y que la balanza número 3 siempre mide alrededor de ocho libras más que las balanzas número 1 y 2. Es razonable asumir que la precisión de las balanzas número 1 y 2 es igual y que una podría medir siempre una pequeña cantidad en déficit del valor verdadero y la otra una pequeña cantidad en exceso del valor verdadero. La balanza número 3 es un caso distinto, ya que con ella se registra siempre un valor bastante mayor que el peso real del niño. Como un resultado de estas consideraciones el modelo siguiente es justificado: Si el valor verdadero del peso es m, entonces la balanza 1 registra el valor m-d, la balanza 2 registra m+d y la balanza 3 registra m+h, donde d y h son constantes positivas que indican el monto de error usual. Siguiendo esta notación, sea m_i el peso real del niño i y p_{ijk} el peso observado

TABLA I: PESOS DE LOS NIÑOS EN LIBRAS, P_{ijk}

Niño	Balanza j			Totales				Pesos estimados
i	1	2	3	$p_{il.}$	$p_{i2.}$	$p_{i3.}$	$p_{i..}$	m_i
1	32.75, 32.50	33.00, 33.00	40.50	65.25	66.00	40.50	171.75	32.70
2	33.50, 33.50	34.00, 34.00	41.75	67.00	68.00	41.75	176.75	33.70
3	35.75, 35.25	36.00, 36.00	44.75	71.00	72.00	44.75	187.75	35.90
4	31.25, 31.25	31.50, 31.50	39.00	62.50	63.00	39.00	164.50	31.25
5	31.50, 31.25	31.75, 31.50	39.75	62.75	63.25	39.75	165.75	31.50
6	34.00, 34.00	34.38, 34.25	42.50	68.00	68.63	42.50	179.13	34.18
7	34.50, 34.50	34.75, 34.75	43.00	69.00	69.50	43.00	181.50	34.63
8	37.38, 37.25	37.38, 37.38	46.25	74.63	74.76	46.25	195.64	37.48
9	33.12, 33.00	33.38, 33.25	41.25	66.12	66.63	41.25	174.00	33.15
10	36.00, 36.12, 34.94	36.38, 36.38		107.06	72.76		179.82	36.02
11	34.25, 34.38, 34.25	34.75, 34.38		102.88	69.13		172.01	34.46
12	42.00, 42.00, 41.88	42.38, 42.25		125.88	84.63		210.51	42.16
	TOTALES			942.07	838.29	378.75	2159.11	

al realizar la medición k en el niño i por medio de la balanza j.

En la Tabla No. 1, $p_{111} = 32.75$, $P_{112} = 32.50$, $p_{121} = 33.00$, $p_{122} = 33.00$ y $P_{131} = 40.50$. Por lo tanto es evidente que fuera del error de medición.

$$P_{ilk} = m_i - d$$

$$P_{i_2k} = m_i + d$$

$$P_{i_3k} = m_i + h$$

donde i=1, 2,....., 12 y k es 1, 2 ó 3, dependiendo de los valores de i y j.

Con los datos de la Tabla I el problema consiste en estimar los pesos reales de los doce niños y los errores d y h. Es evidente que es mejor usar todos los datos para estimar primero los errores d y h y ajustar las medidas por medio de la corrección apropiada. Ya que no queremos desperdiciar información debemos usar los datos registrados con la balanza número 3 aunque es claro que estaba dando datos erróneos.

Una persona con un limitado conocimiento de estadísticas trataría de estimar el peso de cada niño usando el promedio de los cinco pesos observados para ese niño. Esto claramente no es conveniente ya que para el niño número 1 hay una observación de la balanza número 3 que es obviamente incorrecta y entonces esta observación debería descartarse. En el caso del niño número 10, en el que no se realizó una medición con la balanza número 3, existen tres realizadas con la balanza nú-

mero 1 y dos con la balanza número 2. Existe aquí un problema de sezgo ya que la media.

$$(p_{10,1,1} + p_{10,1,2} + p_{10,1,3} + p_{10,2,1} + p_{10,2,2})/5$$

es una estimación de

$$(m_{10} - d + m_{10} - d + m_{10} - d + m_{10} + d + m_{10} + d)/5 = m_{10} - d/5$$

que no es m_{10}, por una inclinación viciada de d/5. Cierto que si d es pequeña, entonces d/5 es más pequeña, pero en todo caso, el simple promedio no parece ser la mejor manera de estimar el peso de cada niño.

Demostraremos que la omisión de medidas con la balanza número 3 en el caso de los últimos tres niños hace imposible estimar su peso usando los métodos usuales de cuadrados mínimos o del máximo de verosimilitud. También será demostrado que de haberse continuado usando la balanza errónea, no tendríamos problema en la estimación.

El método de cuadrados mínimos (1) consiste en encontrar los valores de m_i, d y h que hagan mínima la siguiente suma de cuadrados.

$$T = \sum (p_{ijk} - n_{ij})^2$$

donde $\sum$ indica la suma de todos los valores posibles de i, j y k y $n_{il} = m_i - d$, $n_{i_2} = m_i + d$ y $n_{i_3} = m_i + h$.

Si se hace la suposición usual de que el error de una observación es distribuído normalmente con una variancia v^2 común para todas las observaciones, el método del máximo de verosimilitud (1) consiste en encontrar los valores de las m_i, d y h que maximicen la siguiente expresión:

$$U = (2\pi)^{-n/2} v^{-n} \exp(-T/2v^2)$$

donde T fue ya definido y $\exp(x) = e^x$.

Tenemos en este caso que en cuanto concierne a la estimación de las m_i, d y h, los dos métodos son iguales porque minimizar T es equivalente a maximizar U. Por lo tanto, las ecuaciones que tenemos que resolver para minimizar T o para maximizar U son las siguientes:

$p_{i\,..} = 5m_i + h$, para i = 1, 2, ..., 9,

$p_{i\,..} = 5m_i - d$, para i = 10, 11, 12,

$p_{.1.} + p_{.2.} = 4m_{.} + m_{10} + m_{11} + m_{12} - 3d$, y finalmente,

$p_{.3.} = 5m_{.} - 5(m_{10} + m_{11} + m_{12}) + 9h$

donde "." indica la suma sobre todos los valores posibles. De la solución de este sistema de ecuaciones se obtiene

$$h = (4p_{.3.} - p_{.1.} - p_{.2.} + p_{10..} + p_{11..} + p_{12..})/36 = 296.98/36 = 8.25$$

de modo que las estimaciones de los pesos para los niños números 1 hasta 9 son

$$m_i = (p_{i..} - h)/5.$$

Desafortunadamente estas ecuaciones no tienen solución para d, m_{10}, m_{11} y m_{12} de modo que no podemos estimar el peso de tres niños usando los dos métodos citados. Si el procedimiento usado hubiera sido igual para todos los niños, no tendríamos ningún problema en la solución de las ecuaciones, y podríamos obtener

$h = (4p_{.3.} - p_{.1.} - p_{.2.})/48$,

$m_i = (p_{i..} - h)/5$ para i = 1, 2,...., 12,

aunque todavía no podemos estimar d. Sin embargo, eliminando observaciones es posible obtener una estimación libre de sezgo, así:

$d = (p_{.31} - p_{.11} - p_{.12})/24 = (838.29 - 831.00)/24 = 7.29/24 = 0.30$

Con este valor de d, podemos entonces estimar los pesos de los niños números 10, 11 y 12 por $m_i = (p_i + d)/5$ aunque para estos tres niños sólo podemos afirmar que estas estimaciones son imparciales o libres de sezgo, lo cual es en realidad una propiedad muy débil. La Tabla I presenta los pesos estimados para los niños números 1 hasta 9 por el máximo de verosimilitud, cuadrados mínimos y sin sezgo mientras que también presenta las estimaciones de peso para los niños números 10, 11 y 12, las que solamente son imparciales o libres de sezgo (sin inclinación viciada).

Conclusiones

De lo que antecede es evidente que es necesario un cuidado extremo antes de hacer cambios en métodos o procedimientos.

Hemos considerado un ejemplo de datos incompletos: a tres de los niños les faltaba una observación con la balanza número 3 mientras que a nueve les faltaba una observación con la balanza número 1. El problema de datos perdidos o incompletos es grande y muchas personas opinan que es el más difícil de la estadística. Muy a menudo el análisis estadístico es extremadamente difícil, o bien como en el presente ejemplo, no es enteramente satisfactorio.

Summary

On November 24, 1965 the Pediatritions in the course, International Course of Social Pediatrics, held in Guatemala City went to Children's Home to perform certain anthropometric measurements of the children. We are concerned here with the results of the data of weights taken on three different scales of the twelve children studied. When only three children remained to be weighed, it was observed that scale number 3 was giving values approximately eight pounds too much and, for this reason, it was decided to discontinue use of scale number 3 and use only numbers 1 and 2. This paper will show that to stop using the scale was a great mistake, and it would have been much better to have used scale 3 so that the statistical methods of maximum likelihood and least squares could be applied.

Referencia

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DISCURSO

EL AÑO DE LA OPORTUNIDAD

José A. Alvarez de Choudens, MD

No tengo duda de que cuando yo revise las más importantes experiencias de mi vida dedicada a la medicina, brillará este momento más intensamente que ninguno otro.

Me es imposible expresar claramente los sentimientos que me llenan al asumir la presidencia de la Asociación Médica de Puerto Rico. Debo, por lo tanto, conformarme con decirles "Muchas Gracias" y asegurarles que haré lo mejor que pueda con la ayuda de Dios para mantener la efectividad y la integridad que han dado a este puesto una larga lista de distinguidos y bien recordados predecesores.

Todo lo que haga lo haré con él único propósito de avanzar los altos objetivos de la Asociación Médica de Puerto Rico. Lo que pueda lograrse este año, se logrará solamente porque contaré con el respaldo, con la ayuda y con la oración de todos los miembros de nuestra querida Asociación, y con la ayuda de los otros grupos que componen el equipo de la salud.

Son pocas las veces que unos hombres y mujeres se encuentran en un momento histórico con el potencial de acción que tiene el momento en que vivimos. La medicina en Puerto Rico ha llegado a una encrucijada que nos impone el buscar y encontrar cuál ha de ser el nuevo derrotero. Los últimos años han traido al escenario el concepto de que los servicios de salud no son un privilegio, que la buena salud es un derecho. "En salud se impone calidad y no caridad". Nuestro pueblo ha entendido que no es posible la "mejor calidad de servicios de salud" si no existe "libre selección de médico y hospital".

En su discurso de toma de posesión el 19 de noviembre del año pasado, el doctor Izquierdo Mora repasó los cambios sociales, económicos y a los servicios de salud, ocurridos en Puerto Rico en las últimas tres décadas. El último año ha traído importantes cambios adicionales, algunos de los cuales son:

1— La Junta de Planes acaba de anunciar que el ingreso per cápita rebasó por primera vez los $1,000 por año, el 30 de junio de 1967 llegando a $1,047 por persona y $5,235 por familia de cinco.

Es importante anotar que la Junta de Planificación proyectó en el 1964 que este nivel de ingresos sería conseguido en el 1970. Es motivo de alegría para todos los puertorriqueños que se haya rebasado el nivel de $1,000, tres años antes que lo proyectado hace precisamente tres años.

2— De acuerdo con los estudios de la

Pronunciado en ocasión de la toma de posesión de la Presidencia de la Asociación Médica de Puerto Rico, el 18 de noviembre de 1967, en el Hotel San Juan, San Juan, Puerto Rico.

Junta de Planificación en cuanto a distribución de familias por niveles de ingreso al 30 de junio de 1967, las familias con ingreso menor de $3,000 por año y los individuos que viven solos con ingreso menor de $1,500 anual representan algo menos del 40 por ciento de nuestra población, o sea, alrededor de 1,040,000 personas.

El Informe Trussell-Arbona indicó que en el 1958 el 80 por ciento de nuestra población dependía de las facilidades gubernamentales para sus servicios de salud. A mediados de 1965 nuestro Departamento de Salud calculó que el 65 por ciento de nuestra población tenía ingresos (familia de cinco, menos de $3,000; individuo solo, menos de $1,500 por año) que los clasificaba como médicamente indigentes. Es motivo de gozo para todos el que nuestro progreso económico haya resultado en marcada reducción a 40 por ciento en número de nuestros conciudadanos que por tener ingresos demasiado reducidos no pueden aportar para financiar sus servicios de salud.

3— Las estadísticas sobre la práctica de la medicina en Puerto Rico (año 1966) publicadas por el Dr. Oscar Costa Mandry en abril de 1967, indican que al final del año 1966 practicaban la profesión en Puerto Rico 2,754 médicos, en proporción de un médico por cada 920 habitantes. Es bueno recordar que el Informe Trussell-Arbona, publicado en febrero de 1962, señalaba la proporción de un médico por cada 1,000 ciudadanos como la meta para el año 1970. Es motivo de alegría para todos el que se haya rebasado dicha meta cuatro años antes que lo proyectado.

El progreso experimentado en este renglón en los últimos veinte años ha sido extraordinario, según la Tabla I.

TABLA I: RELACION DEL NUMERO DE MEDICOS A LA POBLACION

Año	Número de Médicos	Habitantes por Médico
1899	174	5,478
1930	359	4,171
1940	456	4,118
1950	908	2,751
1960	1,675	1,666
1966	2,754	920

Podemos tener mejor idea de lo que significa este logro si comparamos con otros países. (Tabla II)

TABLA II: RAZON MEDICO A POBLACION EN VARIOS PAISES

País	Año	Habitantes por Médico
Albania	1963	2,500
Bolivia	1963	3,700
Chile	1960	1,600
El Salvador	1963	4,700
España	1963	820
E. U.	1966	666
Guinea	1961	21,000
Haití	1961	10,600
Inglaterra	1960	960
Jamaica	1963	2,200
Liberia	1964	11,000
México	1960	1,700
Panamá	1964	3,100
Perú	1964	2,200
Portugal	1963	1,200
Puerto Rico	1966	920
Rep. Dominicana	1956	4,800
Suecia	1960	1,000
Uruguay	1962	1,100

4— Se implementó la Ley Federal que provee un seguro médico hospitalario (Título XVIII) para las personas mayores de 65 años, cubriendo en Puerto Rico 158,000 personas.

Se continuó en nuestra Isla la implementación del Título XIX (Medicaid) a través del sistema de salud gubernamental. Pero el informe del comité investigador de nuestro programa Título XIX encontró 16 graves fallas en dicho programa. El Departamento de Salud Federal dio hasta el 1ro. de julio de 1967 para la corrección de dichas fallas. Hasta hoy no tenemos conocimiento de las medidas que se hayan tomado para corregir esta situación por parte del Departamento de Salud.

5— La Asociación Médica Americana aprobó y llevó al Departamento de Salud Federal una resolución de la Asociación Médica de Puerto Rico pidiendo que el Título XIX (Medicaid) fuera enmendado para garantizar a los médicamente indigentes libre selección de médico. Esta medida fue propuesta al Congreso por la administración del Presidente Johnson, y ha sido aprobada por la Cámara de Representantes y el Comité de Finanzas del Senado, garantizando el derecho de libre selección de médico y hospital efectivo en los estados en el 1969 y en Puerto Rico, en el 1972.

Funcionarios de la Asociación Médica de Puerto Rico han hecho ocho viajes a Washington abogando porque no se privara a nuestros ciudadanos pobres de este derecho.

6— La Asociación Médica de Puerto Rico abogó por la liberalización en el uso de los fondos federales Hill-Burton. De dichos fondos se asignaron 19 por ciento en los años 1966 y 1967 para la construcción de hospitales de la comunidad.

7— Ha habido un aumento considerable en las personas acogidas a seguros médicos. Los mejores números disponibles al presente se presentan en la Tabla III.

TABLA III: PERSONAS ACOGIDAS A SEGUROS MEDICOS

Programa de Servicios	Número de Personas
Cruz Azul de Puerto Rico	150,000
Seguros de Servicios de Salud (SSS)	125,000
Cooperativa de Salud	50,000
Asociación de Maestros	38,000
Plan Servicio Médico Hospitalario	80,000
Medicare (Título XVIII)	158,000
Auxilio Mutuo	8,700
Compañías Seguros Comerciales	150,000
Uniones Obreras	200,000
Veteranos	132,000
Empleados Federales	5,000
Total	1,096,700

Al añadirse a este número el diez por ciento de la población, que se calcula paga directamente (260,000 personas), la suma es 1,356,700 personas; o sea, más del 50 por ciento de nuestra población.

8— Se aceleró el programa de construcción de facilidades hospitalarias gubernamentales, adelantándose la construcción del Centro Médico de Mayaguez, y la planificación de los hospitales subregionales de Caguas y Bayamón, entre otros. Los fondos para este programa han sido aumentados con el producto de los nuevos impuestos sobre cigarrillos y licores.

Estas y muchas cosas más han ocurrido en Puerto Rico en el pasado cercano, que hacen que el momento que vivimos tenga extraordinario potencial de acción. Por lo recientemente pasado, y porque se avecinan elecciones generales, se perfila el 1968 como

el "Año de la Oportunidad".

El año 1968 nos ofrece la oportunidad de llevar a feliz conclusión nuestro empeño en conseguir que todos nuestros ciudadanos gocen del derecho a seleccionar el médico de su fe y confianza.

Al hablar con legisladores y funcionarios gubernamentales encontramos una actitud filosófica favorable al principio de libre selección. Pero encontramos la casi unánime opinión de que este principio no puede aplicarse en Puerto Rico por falta de fondos. Nos dicen funcionarios del Gobierno de Puerto Rico:

"Son muchos los que no pueden pagar por los servicios médicos privados y, por lo tanto, dependen del gobierno"; y añaden, "Los servicios médicos privados son mucho más caros". Se dice y nos ha sido repetido durante esta semana por altos funcionarios de nuestro Departamento de Salud, que el 65 por ciento de nuestra población tiene ingresos que los clasifican como médicamente indigentes.

Ante esto me pregunto yo, ¿Es que las estadísticas significan algo para la industria, el comercio y la economía y algo distinto en el campo de la salud? Si nuestro ingreso per cápita pasó ya de los $1,047 por persona y de $5,235 por familia de cinco, ¿por qué se sigue diciendo que el 65 por ciento de nuestra población sigue siendo médicamente indigente?

En su ponencia ante el Comité de Medios y Arbitrios de la Cámara de Representantes en abril de 1967, nuestro Comisionado Residente en Washington declaró que "el costo de los servicios médicos privados en Puerto Rico es por lo menos cuatro veces más alto que el de los servicios médicos públicos" y que por esta razón se debía eximir el programa Título 19 de Puerto Rico del requisito de libre selección. Utilizando la estadística ya disponible en aquella fecha, pudimos probarle al Honorable Comisionado Residente que tal aseveración era contraria a la evidencia, razón por la cual él pidió al Congreso que se ordenara al Departamento de Salud, Educación y Bienestar Federal que hiciera estudios para determinar la fecha en que sería factible la libre selección de médicos en Puerto Rico.

Para vuestra consideración ofrezco la más reciente información sobre costos de servicios médico-hospitalarios disponible a nosotros. Véase tablas IV,V,VI, y un resumen de éstas en la Tabla VII.

Esta información repudia la aseveración de que "los servicios médicos privados son mucho más caros que los públicos", y mucho menos el que son "por lo menos cuatro veces más costosos que los servicios médicos públicos". Esta información refuta la "casi unánime opinión de que el principio de libre selección no puede aplicarse en Puerto Rico por falta de fondos". El análisis profundo de esta información ofrece a nuestro gobierno la oportunidad de financiar estos servicios para nuestros ciudadanos médicamente indigentes de manera que se les asegure el derecho a libre selección de médico y facilidades de salud.

El análisis de estadísticas del Departamento de Salud nos dejó ver interesantes diferencias de la relativa eficiencia en la utilización de las facilidades hospitalarias. Creimos conveniente efectuar una comparación de utilización entre los cinco hospitales regionales (gubernamentales) y hospitales generales no-gubernamentales y para esto utilizamos las estadísticas sometidas por estos hospitales al American Hospital Asso-

TABLA IV: LABOR REALIZADA POR LOS HOSPITALES REGIONALES GUBERNAMENTALES,AÑO 1966-67

Datos	Aguadilla	Arecibo	Fajardo	Ponce	Río Piedras	Total
Complemento de camas	280	280	280	412	348	1595
Admisiones (casos hospitalizados)	11,457	9,722	8,316	12,195	13,344	55,034
Por ciento Ocupación	100.9	89.7	82.8	93.7	92.3	92.1
Estadía promedio (días)	9.0	9.3	10.2	11.6	8.7	9.7
Costo por día (promedio)	$14.09	$14.11	$14.81	$17.60	$49.05	$22.67
Costo por caso (promedio)	$126.81	$131.22	$151.06	$204.16	$426.74	$220.79
Costo por visita a clínica externa	$5.06	$5.69	$10.59	$8.08	$9.79	$7.04
Costo por visita a sala de emergencia	$2.66	$7.70	$12.71	$5.99	$14.41	$7.88

Nota: Esta información fue tomada del Informe Anual del Departamento de Salud (en prensa) del 1966-67.

ciation para el año 1966, según aparecen en el Guide Issue del Journal of the American Hospital Association, de agosto 1ro. de 1967. Son éstas las únicas estadísticas recientes de la labor de los hospitales gubernamentales y no-gubernamentales presentada en forma comparable. (Véase Tabla IX).

La Tabla X resume la labor realizada durante el año fiscal 1966-67 por los hospitales regionales gubernamentales, y el año natural 1966 por ocho hospitales no-gubernamentales. Los ocho hospitales no-gubernamentales con un total de 937 camas atendieron 51,955 pacientes hospitalizados mientras que los cinco hospitales regionales con 1,595 camas atendieron 55,034 pacientes hospitalizados. ¡Los ocho hospitales no-gubernamentales contando con menos del 60% de camas (comparado con los hospitales regionales gubernamentales) atendieron casi el mismo número de pacientes hospitalizados (5% menos) que los hospitales regionales!

La explicación está en que los hospitales regionales necesitaron ocupar una cama 9.7 días por cada caso hospitalizado, mientras que los ocho hospitales no-gubernamentales, solamente necesitaron usar una cama 6 días por caso hospitalizado.

Se puede llegar a la conclusión de que la utilización de una cama en un hospital no-gubernamental es muy significativamente más eficiente que la utilización de una cama

TABLA V: ESTADISTICAS DEL PLAN DE HOSPITALIZACION Y SERVICIOS MEDICOS DE LA CRUZ AZUL DE PUERTO RICO

Datos	1964	1965	1966
Casos Hospitalizados	20,010	26,642	23,596
Estadía promedio (días)	6.33	6.12	6.01
Costo por día	$24.83	$26.00	$29.83
Costo por caso	$157.10	$160.00	$155.22

Nota: Esta información fue tomada del informe anual de la Cruz Azul de Puerto Rico para el año 1966, según presentado al Comisionado de Seguros del ELA.

TABLA VI: ESTADISTICAS DEL PLAN DE HOSPITALIZACION Y SERVICIOS MEDICOS DE "SEGUROS DE SERVICIO DE SALUD" (S.S.S.)

Datos	1964	1965	1966
Casos hospitalizados	11,871	12,063	13,844
Estadía promedio (días)	6.12	6.07	5.84
Costo por día (Hosptalización solamente)	18.69	18.82	20.23
Costo por caso (Hospitalización solamente)	$114.42	$114.22	$118.07
Costo por día (Servicios médicos y hospitalización)			27.47
Costo por caso (Servicios médicos y hospitalización)			162.42
Visita clínica externa (en la oficina del médico)			4.73

Nota: Esta información fue tomada de los informes anuales de SSS para los años 1964, 1965 y 1966 según presentados al Comisionado de Seguro del ELA con excepción de los tres últimos renglones que fueron calculados por SSS a petición nuestra.

TABLA VII: COSTOS DE LOS HOSPITALES REGIONALES, GUBERNAMENTALES, CRUZ AZUL DE PUERTO RICO Y SEGUROS DE SERVICIOS DE SALUD (S.S.S.)

	Hospitales Regionales Gubernamentales		Cruz Azul de Puerto Rico	SSS
Datos	1965-66	1966-67	1966	1966
Casos hospitalizados	53,355	55,034	23,596	13,854
Estadía promedio (días)	10.0	9.7	6.01	5.84
Costo por día (Servicios médicos y hospitalización)	$18.81	$22.67	$29.83	$27.47
Costo por caso (Servicios médicos y hospitalización)	$188.10	$220.79	$155.22	$162.42

Nota: Tomada de las tablas I, II y III.

TABLA VIII: LABOR REALIZADA POR LOS HOSPITALES DE PSIQUIATRIA (CLINICA EXTERNA)

	Río Piedras		Ponce	
Datos	1965-66	1966-67	1965-66	1966-67
Visitas a clínicas externas	35,165	53,612	14,795	17,515
Costo visita clínica externa	$18.53	$19.96	$21.42	$14.14

Nota: Información tomada de los informes anuales del Departamento de Salud 1965-66 y 1966-67

TABLA IX: LABOR REALIZADA POR EL HOSPITAL DE TUBERCULOSIS DE BAYAMON (CLINICA EXTERNA (2)

Datos	1965-66	1966-67
Visitas a clínica externa	3,136	4,406
Costo visita a clínica externa	$22.27	$19.32

Nota: 1) Esta información fue tomada de los informes anuales del Departamento de Salud para 1965-66 y 1966-67.

2) Los servicios de clínica externa no se ofrecen en otros hospitales de tuberculosis.

TABLA X: UTILIZACION DE OCHO HOSPITALES NO GUBERNAMENTALES QUE SIRVEN A SUSCRIPTORES DE SSS Y DE LA CRUZ AZUL DE PUERTO RICO (1966)

	Bellavista Mayaguez	Perea Mayaguez	Clínica Dr. Pila Ponce	San Lucas Ponce	Presbiteriano Santurce	Pavía Santurce	Del Maestro H. Rey	Ryder Memorial Humacao	Total
Número de camas	82	107	130	101	200	100	130	112	937
Casos hospitalizados	4,283	4,792	7,153	5,930	11,250	7,074	7,573	3,900	51,955
Por ciento de ocupación	85.4	78.7	91.5	90.1	93	93	96.2	87.8	90%

NOTA: Esta información fue tomada del Guide Issue del Journal of The American Hospital Association de agosto de 1967.

TABLA XI: UTILIZACION (COMPARADA) DE LOS CINCO HOSPITALES REGIONALES 1966-67 Y OCHO HOSPITALES PRIVADOS (1966)

Datos	Regionales	Privados
Número de camas	1,595	937
Por ciento de ocupación	92.1%	90%
Casos hospitalizados	55,034	51,955
Días por caso	9.7	6

en un hospital regional gubernamental.

La Tabla XI resume la labor de los centros de salud y la Tabla XII combina la estadística de éstos con la de los hospitales regionales gubernamentales. Notarán que en el 1966-67 el porciento de ocupación de los centros de salud fue de solo 62%. Es bueno aclarar que aunque ya hace varios años que se abrió el Centro Médico de Ponce todavía hay 70 camas que no están siendo utilizadas y que no son incluídas en los informes del Departamento de Salud que hemos citado.

Estas estadísticas indican que las camas gubernamentales están operando a un nivel de eficiencia bajo. Si fueran utilizadas todas las camas (incluyendo las 70 de Ponce) a un nivel de ocupación de 85 a 90% con una estadía promedio de 6 días, se podrían atender en las camas gubernamentales hoy disponibles de 40 a 50% más pacientes. Nos parece razonable predecir que

TABLA XII: LABOR REALIZADA POR LOS CENTROS DE SALUD

Datos	1965-66	1966-67
Complemento de camas	1,660	1,687
Admisiones (casos hospitalizados)	66,098	65,006
Días (paciente) producidos	382,513	381,746
Por ciento ocupación	64.3%	62.0%
Estadía promedio (días)	5.8	5.9
Costo por día	no ha sido publicado	
Costo por caso	no ha sido publicado	

desaparecerían las listas de espera y especular que no sería necesario construir todas las camas que han sido proyectadas.

En su discurso de toma de posesión, mi antecesor, el querido compañero, Dr. Luis A. Izquierdo Mora, presentó cincuenta puntos como las metas de su plan de acción durante su presidencia. Algunas de ellas tales como la legislación para permitir los matrimonios de epilépticos, y la ley para prohibir el uso de la droga LSD, el problema de los exámenes en inglés a los graduados de universidades extranjeras y el garantizar la libre selección de médico a los beneficiarios del Título XIX han sido o están ya en franca vía de solución. El resto del plan de acción representa el programa de nuestra Asociación Médica de Puerto Rico y yo lo abrazo con todo entusiasmo y pido vuestra ayuda para lograr su culminación.

El año que acaba de pasar ha ampliado los horizontes de nuestra Asociación. Han surgido nuevos problemas y otros han cambiado de perspectiva. Para el año que empieza debemos dar especial atención e interés a los siguientes:

1. Desarrollo de un programa del Corazón, Cáncer y Apoplejía cooperando con la Escuela de Medicina, el Departamento de Salud, hospitales de la comunidad, grupos voluntarios y otros.

2. Respaldaremos la iniciativa de nuestro distinguido expresidente, Dr. Ramón M. Suárez, propulsando la candidatura del eminente cardiólogo y amigo de Puerto Rico, el Dr. Paul Dudley White, para el premio Nobel de la Paz para 1968.

3. Continuaremos laborando para que la Cruz Azul y el Escudo Azul de Puerto Rico se conviertan en planes azules convencionales con funciones separadas verticalmente y laborando en estrecha cooperación.

4. Continuaremos propulsando el sistema de seguro médico prepagado voluntario me-

TABLA XIII: LABOR (COMBINADA) REALIZADA POR LOS HOSPITALES REGIONALES Y GUBERNAMENTALES Y LOS CENTROS DE SALUD (AÑO 1966-67)

Datos	Centros de Salud	Hospitales Regionales	Total
Complemento de camas	1,687	1,595	3,282
Admisiones (casos hospitalizados)	65,006	55,034	120,040
Por ciento ocupación	62%	92.1%	75.7%
Estadía (promedio) días	5.9	9.7	7.64

diante el cual todos nuestros ciudadanos puedan gozar de la mejor calidad de servicios médicos con libre selección de médico y facilidad hospitalaria, basado en el principio de que nuestro gobierno debe ayudar a cada ciudadano en proporción a sus medios económicos.

5. Propulsaremos la reorganización del Departamento de Salud para que nuestro pueblo pueda contar con los mejores servicios en las distintas áreas de responsabilidades de dicha agencia.

A— Propulsaremos la creación de un Departamento de Salud Mental.

B— Propulsaremos la creación de un Departamento de Bienestar Público o Social.

C— Pediremos el fortalecimiento de la división correspondiente para que se ejerza a cabalidad la función reguladora y fiscalizadora en cuanto a hospitales, casas de salud, farmacias, laboratorios, alimentos, mataderos, máquinas de Rayos X, y otros más.

D— Pediremos el fortalecimiento de la División de Salud Ambiental para que se bregue con máxima eficiencia con los problemas de contaminación de agua y aire, insectos, parásitos, accidentes, enfermedades venéreas, tuberculosis, vacunación y muchos otros.

E— Propulsaremos la conversión de hospitales gubernamentales a hospitales de la comunidad.

6. Propulsaremos un programa Hill-Burton puertorriqueño que facilite la construcción de hospitales de la comunidad sin fines de lucro mediante la aportación de fondos estatales en proporción a los fondos contribuídos por la comunidad.

7. Propulsaremos, que allí donde haya escasez de camas y no se logre construir un hospital de la comunidad, se instrumente la Operación Manos a la Obra de nuestro gobierno ofreciendo a los interesados en construir hospitales privados los mismos incentivos que se ofrecen actualmente a las industrias nuevas.

8. Propulsaremos la creación de una Junta Estatal de Salud, con adecuada representación de la comunidad y de los proveedores de servicios de salud.

9. Continuaremos laborando para que en materia de salud y bienestar público Puerto Rico reciba trato igual al de los estados federados. Para esto iremos a Washington cuantas veces sea necesario.

Conclusion

El año 1968 nos trae la oportunidad de grandes logros en el campo de la salud. A nosotros los médicos ofrece la realización de nuestra misión. A nuestros conciudadanos necesitados ofrece el acceso a la mejor calidad de servicios de salud a través de la libre selección de médico.

Compañeros, renovemos nuestra dedicación a esta meta, llevemos el mensaje de nuestra Asociación a todo lo ancho y todo lo largo de Puerto Rico. ¡A garantizar la salud de nuestro pueblo en el año 1968, el que yo he llamado, El Año de la Oportunidad! Dediquemos nuestros esfuerzos con el favor de Dios, a que Puerto Rico logre esa oportunidad que es suya, por ser oportunidad de nosotros los médicos.

CASE REPORTS

PHEOCHROMOCYTOMA

Germán E. Malaret, MD
José E. López, MD

Pheochromocytomas are uncommon tumors for which we physicians are always searching. The reason is obvious. When one is found in a hypertensive patient, and it is removed, the results are usually extremely gratifying. The diagnosis, treatment and surgical removal of these tumors, however, is not easy or without hazards.

Recently, we were fortunate in finding such a case of pheochromocytoma. It was decided to present it to remind you of the existence of these tumors and stimulate the continuous search for them, review the diagnostic tests available, review the hazards faced at surgery and discuss the pertinent literature.

Case Report

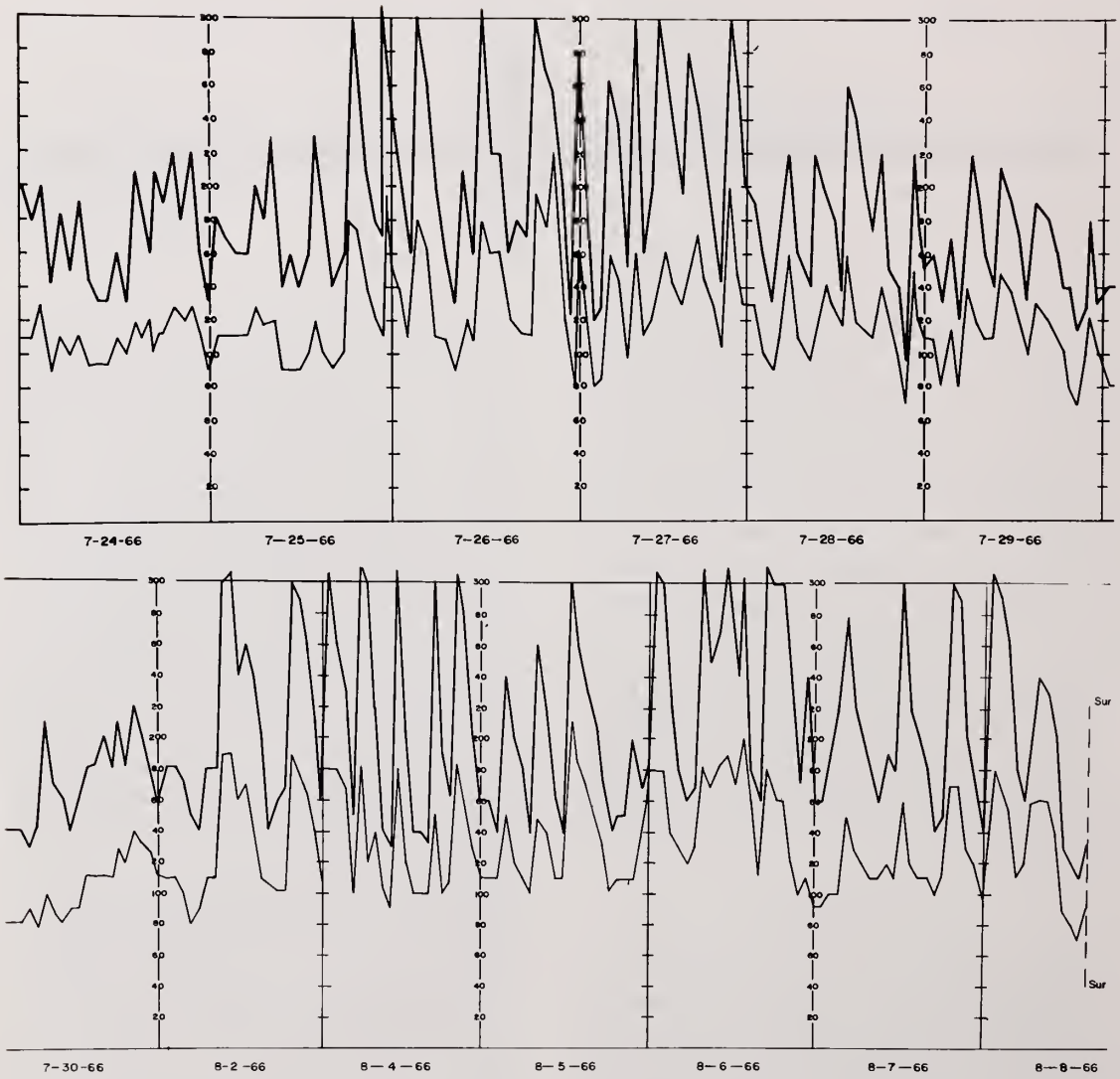
A 64-year-old white male was admitted because of chest pain and headaches. For eight years he had had mild hypertension which had progressed to moderate hypertension. At first he was treated with sedatives with good results. Because of the increase in the blood pressure, he was started on guanethidine three years before we saw him. During the last two years he had developed paroxysmal attacks characterized by palpitations, severe headaches, profuse sweating, market pallor, dizziness and severe substernal chest pain radiating to his navel and suprapubic area. The episodes occurred on exercise, on changes in position and when anxious, but most frequently on standing and voiding. They would last one to three minutes and would subside on lying down although the pallor and substernal aching would persist for some time. He would feel exhausted after each attack. These were infrequent at first, but they gradually increased in frequency. As the blood pressure rose the guanethidine dose was raised and he was placed on diuretics. About two to three weeks before admission the blood pressure was recorded at 260/130 mm Hg. Studies done elsewhere were unrevealing. On returning home he again suffered with the above attacks and on one occasion had transient loss of consciousness resulting in a fall which produced a contusion on his forehead. At that time he was on 25 mg of guanethidine daily. He was seen by a physician who recorded a blood pressure of 220/110 mm Hg in the evening and gave him and additional 25 mg tablet of guanethidine. The next morning he was referred to us.

Additional history revealed that he had been a mild diabetic for about eight years. He had a strong family history of diabetes and hypertension. Eight years before he had undergone a prostatic transurethral resection without complications.

On admission to the hospital he appeared well nourished and well developed but very tense and anxious. His blood pressure was 220/110 mm Hg supine and 110/80 mm Hg sitting. The skin was pale and sweaty. Funduscopic examination revealed moderate narrowing and increased tortuosity of the arterioles. The aortic second sound was accentuated. The remainder of the examination was unremarkable.

The initial impression was that he was having postural hypotension secondary to the guanethidine therapy and he was taken off all therapy. Diagnostic tests were scheduled and the blood pressure was carefully charted (Fig. 1). There were wide

Presented at the 1967 Annual Meeting of the Puerto Rico Heart Association.



fluctuations in the blood pressure with hypertensive crises noted primarily on micturition, straining at stool and on standing for a few minutes. A few of the paroxysms occurred upon turning in bed. The highest blood pressures were unknown since the sphygmomanometer reached only to 320 mm of mercury. He was observed during several of the crises which closely paralleled his description of them. During these episodes he became extremely pale, sweaty, restless developed substernal chest pain and frequent premature systoles. Postural hypotension of 60/50 mm Hg on standing was also recorded and was usually followed by a hypertensive crisis.

It promptly became evident that he was not having postural hypertension secondary to guanethidine therapy but rather that he probably had a pheochromocytoma with a paradoxical response to the ganglionic blocker. A phentolamine (Regitine ®) test was attempted but could not be carried out due to the instability of the blood pressure. Repeated electrocardiograms showed only

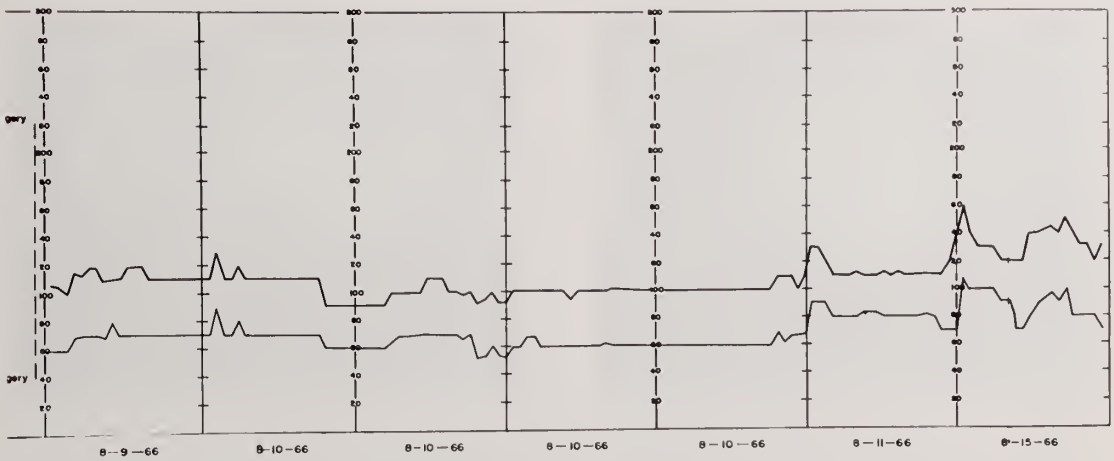


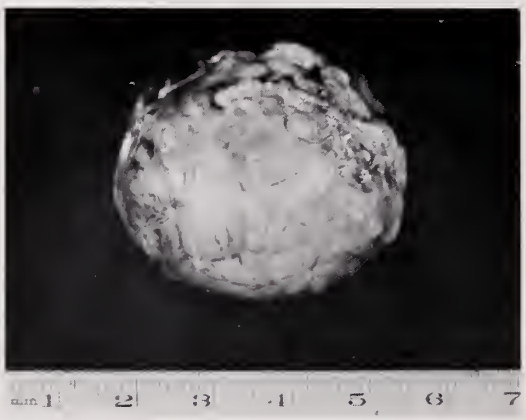
Fig. 1: Blood pressure record. Note that surgery was done on Aug. 9, 1966 and the presence or relative hypotension during the sixty hours immediately following the operation.

non-specific ST-T wave changes and probable left ventricular hypertrophy. A chest x-ray and an intravenous urogram were normal. Twenty-four-hour urinary catecholamines measured 841 and 390 mg. A glucose tolerance test was abnormal with a high value of 290 mgs.% at two hours. The hemogram, cholesterol, blood urea nitrogen, serum lactic dehydrogenase, glutamic oxaloacetic transaminase, sodium and potassium were normal. The initial urinalysis showed a 4+ albuminaria but two other analyses were normal. Two vanillylmandelic acid determinations were normal. An intravenous nephrotomogram (Fig. 2) revealed a 4 cm mass in the region of the right adrenal gland. With the information at hand the diagnosis of pheochromocytoma appeared certain. Oral phentolamine 50 mg every six hours was started and exploratory surgery was carried out two weeks after admission with successful removal of the tumor found in the right adrenal gland. As expected, several moderate hypertensive crises developed on intubation, incision, palpitation of the mass and on ligation of the veins. Each was easily controlled with variable amounts (5-10 mg) of phentolamine intravenously. In addition, a continuous drip of 500 ml of 5% dextrose in water with 50 mgs. of phentolamine had been started at the beginning of surgery. Upon removal of the tumor, the blood pressure began to drop reaching a level of 80/0 mm Hg at which time a Levophed® infusion was started. At the same time 500 ml of whole blood were infused rapidly. The blood pressure promptly stabilized at about 110/70 mm Hg. Thereafter, no further problems were encountered and the post-operative course was uneventful. The Levophed® infusion was discontinued within four hours and no further blood pressure support was required. The pathological examination confirmed the diagnosis of pheochromocytoma. The tumor weighed 35.7 g (Fig. 3). On discharge one week later he was feeling well.



Fig. 2: Intravenous nephrotomogram. Note 4.0 cm mass above superior pole of right kidney.

The patient has been seen at regular intervals after discharge from the hospital and he has remained asymptomatic. A glucose tolerance test and two postprandial blood sugars on different dates have been normal. Two 24-hour urines were collected for catecholamines two days and, again,



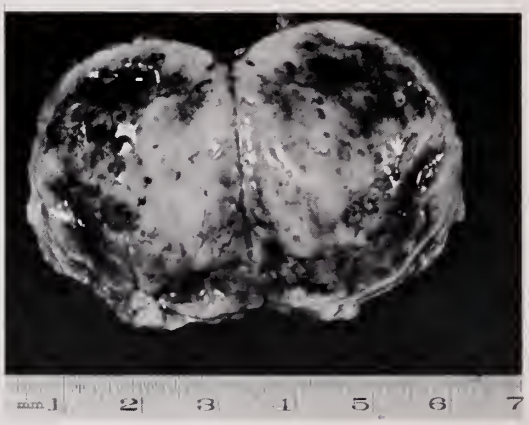


Fig. 3: a) Tumor mass as removed. b) Tumor cut in half.

three months after surgery revealing levels of 132 and 72 mg in 24 hours. The blood pressure has remained at a level of about 150/90 mm Hg. At present it appears that he has been cured of his disease.

Discussion

A review of the literature by Hume (1) revealed that in 1886 Frankel reported the first case of pheochromocytoma. In 1926 Vázquez and Donzelot described the first clinically diagnosed case and later that year Roux, in France, first successfully removed one such tumor. In 1922 Labbé *et al* (2) first related paroxysmal hypertension to these tumors. It wasn't until 1929, however, that Pincoffs (3) first diagnosed a functioning pheochromocytoma clinically, followed by successful removal of the tumor. The relation between these tumors and sustained hypertension was shown by Binger and Craig (4) and by Palmer and Castleman (5) in 1938. Multiple studies between 1929 and 1950 clearly proved the presence of epinephrine and norepinephrine in the adrenal medulla and in adrenergic nerve fibers, their relation to blood pressure and other metabolic functions, and, consequently, the relation between pheochromocytomas, hypertension, and related metabolic alterations. Also during this time, and primarily in the past 15 years refined diagnostic tests were developed to help establish the presence of these tumors. In addition, the drug phentolamine (Regitine) was developed and its use in the diagnosis and treatment of pheochromocytomas described (6).

Histologically, pheochromocytomas are tumors composed of various chromaffin-type cells which may occur anywhere in the body. These tumors are usually classified according to the predominant cell. They may be functioning or non-functioning and, of course, the former are the clinically important ones. They are usually benign and occasionally malignant with a reported incidence of malignancy of 2.8% (1). The tumors are usually found in the adrenal glands and less frequently along the abdominal aorta, but they may occur anywhere. Their reported locations is shown in Table I. It is interesting to note that there have been nine reported instances of familial pheochromocytomas totaling 22

TABLE I: LOCATION OF PHEOCHROMOCYTOMAS

Site	Frequency (%)
Right Adrenal	50-66
Left Adrenal	33-40
Extra Adrenal	10
Bilateral in Adrenals	5.3-9
Multiple Sites	1-1.5

cases and that there were 11 cases of multiple tumors in this group (1). The reported incidence of pheochromocytomas has varied from 0.32-2% of all hypertensives.

Many clinical syndromes have been described in association with these tumors, but in reality they can all be limited to two main syndromes as recommended by Priestley *et al* (7): those with paroxysmal and those with persistent hypertension. As the name implies, the former group is characterized by "attacks" or "episodes" of hypertension frequently associated with other signs and symptoms (see Table II); whereas in the latter the hypertension is persistent although paroxysms of more severe hypertension may occur frequently associated with the signs and symptoms listed in Table II. Paroxysms of hypertension may be precipitated by any number of causes such as micturition, sneezing, changes in position, intercourse, physical effort and many others. The paroxysms are variable in duration and frequently while the intensity tends to be fairly constant; what does change is that paroxysms tend to become more frequent as time passes. The age distribution of these tumors has varied from five months to 82 years but most cases have occurred between 25-50 years of age. In children, the sustained hypertension syndrome is more frequent and this

TABLE II: SIGNS AND SYMPTOMS IN PHEOCHROMOCYTOMAS

Symptoms	Frequency (%)
Headache	81
Sweating	68
Nausea and Vomiting	56
Visual Changes	44
Weight Loss	44
Abdominal Pain	35
Nervousness and Palpitations	34
Weakness and Fatigue	27
Pallor	27
Polyuria and Polydipsia	25
Convulsions	23
Dyspnea	16
Puffy Red Cyanotic Hands	11
Constipation	8
Epistaxis	4
Polyphagia	3
Signs	
BMR>+ 20%	83
Eyeground Changes	77
FBS> 120 MGS%	40
Glycosuria	3
Neurofibromatosis	1.4

is also true in the older age groups. There has been no appreciable sex difference in most series but Priestley et al (7) reported the persistent hypertension syndrome more common in women.

There are several interesting findings about these tumors that are frequently not fully appreciated. For instance, postural hypotension is a common phenomenon among these patients, and this finding plus excessive perspiration in an untreated hypertensive patient strongly suggests pheochromocytoma until proven otherwise. Why this is so, is not clear. These patients frequently respond paradoxically to ganglionic blockers. Our patient showed both of these findings. The tumor may manifest itself during surgery, following trauma or during

a pregnancy. In the latter instance they may appear as severe pre-eclampsia, typical paroxysmal hypertension, headaches without hypertension, sudden shock and death and hyperpyrexia post partum. Therefore, in any pregnant woman who develops hypertension in the first trimester; headaches, vomiting or increased sweating during the last trimester; shock or hypertension during delivery or immediate post partum period or hyperpyrexia post partum, and in those with pre-eclampsia and toxemia, appropriate studies should be carried out to rule out the presence of this curable tumor. At surgery, these tumors make themselves known by sudden hypotension, hypertension or shock.

In view of all this, what patients should be primarily screened for the presence of a pheochromocytoma? A review of the literature suggests several groups in particular. Needles to say, all hypertensive patients should be screened for pheochromocytomas but in particular patients who have hypertension and: (1) "peculiar" attacks, (2) diabetes, (3) an increased basal metabolic rate or clinical hypermetabolism with normal serum cholesterol level, protein bound iodine and ^{131}I uptake, (4) are children without renal or cardiovascular disease, (5) postural hypotension, vasomotor phenomena, increased sweating or increased temperature, (6) are pregnant with the syndromes described above, (7) neurofibromatosis, (8) a familial history of pheochromocytoma, (9) a previously removed pheochromocytoma, (10) show weight loss or failure to gain weight in a thin person, (11) show progression of their disease, or a sudden change from benign to malignant hypertension, or fluctuating blood pressure levels.

It is evident from the above discussion that the history is of paramount importance in these patients. The physical findings are usually not striking with the exception of hypertension unless one witnesses one of the paroxysms of hypertension. Sometimes an "attack" or rise in blood pressure can be precipitated by palpation of the adrenal areas or by one of the motions known to provoke these episodes. The latter was the case in the patient described here in that micturition and changes in position would cause the attacks. Once the suspicion is present several tests should be carried out. These include a basal metabolic rate which is elevated in about 50-83% of the cases, a glucose tolerance curve which is abnormal in about 40% of cases and an intravenous urogram with tomography to look for adrenal masses. A 24-hour urine for catecholamines is mandatory. Values in excess of 300 μg. per 24 hours are usually diagnostic of pheochromocytomas. Plasma catecholamines can also be done. Either of these two tests may be altered by the presence of uremia, tetracycline therapy, jaundice, lymphomas, increased intracranial pressure, the use of nebulizers containing epinephrine and drugs containing methyldopa derivatives. Urinary vanillylmandelic acid may be measured as a screening test but it is not as accurate as the above two tests. The special tests include the phentolamine test, the tyramine test and the histamine plus cold pressor provocative test. All three of these are screening tests since many false positives and false negatives tests may occur. Once the diagnosis is made, tumor localization should be attempted if the con-

dition of the patient permits it. As mentioned above, an intravenous urogram and/or a nephrotomogram is mandatory. Presacral air insufflation and aortography can also be done but these latter two tests are poorly tolerated by these patients and they really add little so that exploratory surgery must be resorted to. Fortunately, 99% of these tumors are found in the abdominal cavity (8).

In our particular case, the catecholamines were in the diagnostic level and, in addition, the patient had a diabetic glucose tolerance curve. Although a basal metabolic rate was not determined, clinically he was obviously hypermetabolic. A phentolamine test was attempted but a sufficiently stable blood pressure was never obtained to carry out the test. The provocative tests were unnecessary. The intravenous urogram was normal, but the nephrotomogram was diagnostic of a mass in the area of the right adrenal gland. With this information available, exploratory surgery was carried out successfully.

It must be remembered that several complications may appear at surgery, the main two being a sudden severe hypertensive crisis and a sudden hypotensive shock state. The former occurs as a result of inadequate pre-operative preparation and failure to control the blood pressure with adequate amounts of phentolamine intravenously during surgery. It is mandatory to have adequate amounts of phentolamine on hand for each case varies greatly in its demands for this drug. The surgeon must also be aware of this problem and must explore with care, stopping the operation as often as necessary to maintain adequate control of the blood pressure. The hypertensive crises occur primarily when intubation for anesthesia is carried out, when surgery is begun, when the tumor is palpated and when its vessels are being ligated. The techniques involved in the removal of these tumors are well described by Hume (1), Priestley et al (7), Sjoerdsma and associates (8) and Cahill and Papper (9).

Once the last vein of the tumor is ligated, hypotension may rapidly develop necessitating the use of a hypertensive agent for appropriate maintenance of the blood pressure. The hypotensive state may last for one to three days postoperatively and continued observation of the blood pressure is necessary. The cause of the hypotension has not been adequately explained, but one factor frequently mentioned is hypovolemia. Sjoerdsma et al (8), however, have clearly shown that this is not the case. Indeed, they have shown that although hypovolemia may accompany pheochromocytomas, particularly malignant ones, the blood volume is usually normal. Thus, adequate replacement of blood loss is often the only thing needed to control the blood pressure. The volemic state can be easily checked by means of a central venous pressure catheter to avoid overhydration or underhydration.

A word about patients who cannot be operated on or who have metastatic carcinomatosis due to a malignant pheochromocytoma. The recent studies at the National Institute of Health by Sjoerdsma and associates (8) have shown that these patients can be successfully controlled with the use of phentolamine or phenoxybenzamine over prolonged periods of time. They prefer phenoxybenzamine because of less

side effects and less frequency of dosages.

Again, in our particular case, surgery was fortunately successful and without serious complications. The hypertensive crises, did occur at intubation, initial incision, on palpation of the tumor and during ligation of the veins. Each episode was easily controlled by the intravenous administration of 5-10 mgs. of phentolamine as needed. As soon as the last vein from the tumor was ligated, the blood pressure began to drop to hypotensive levels. Being aware of this complication, blood was rapidly transfused and Levophed® started with control of the blood pressure. The hypertensive agents were stopped four hours after surgery was completed without trouble although in retrospect, the patient was in "relative" hypotension for about 60 hours after surgery (see Fig. 1). Since the urine output was adequate, close observation alone sufficed and he recovered uneventfully.

It is of interest that his hypermetabolic and diabetic states have disappeared. The catecholamines have been checked twice since surgery and have remained normal. Thus, it appears that the tumor must have been present for about 6-8 years causing the mild diabetes and gradually causing the paroxysmal hypertension. At the present time he is asymptomatic, leading a completely normal life.

Summary

An interesting case of a functioning pheochromocytomas has been presented. The case is interesting because (1) it occurred in a 64-year-old, overweight man, (2) it illustrated the paradoxical response to a ganglionic blocking agent, (3) it illustrated the frequent association between these tumors and metabolic alterations, (4) it showed some of the complications frequently seen during surgery and their control, and (5) it showed the value of the nephrotomogram. In addition the pertinent literature was reviewed and the available diagnostic tests briefly discussed.

Resumen

Se hà presentado un caso de un feocromocitoma activo. El caso es interesante porque (1) ocurrió en un hombre obeso de 64 años, (2) ilustra la respuesta paradójica de estos tumores a los bloqueadores gangliónicos, (3) ilustra la frecuente asosiación con alteraciones metabólicas, (4) demuestra alguna de las complicaciones que se ven durante cirugía y su tratamiento y (5) demuestra el valor del nefrotomograma. La literatura pertinente ha sido revisada y los estudios diagnósticos disponibles han sido brevemente discutidos.

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NEPHROTIC-UREMIC SYNDROME IN SICKLE CELL DISEASE

Julio V. Rivera, MD FACP
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The renal pathology in sickle cell disease has been described in detail in several reviews of the subject (1, 2, 3). Initially glomerular congestion and enlargement is seen which over the years is followed by the appearance, in some areas, of ischemia, thickening of basement membrane, fibrosis and obliteration of glomeruli. Associated tubules show scarring and obliteration particularly in the region of the pyramids. Normal tissue is found interposed. Focal pyelophritis is a frequent accompanying lesion. Papillary necrosis may occur (4). It is of clinical interest that these findings may occur in the heterozygous form of sickle cell disease, in the absence of anemíia.

Although thromboses in the renal vessels do not usually occur, it seems likely that functional blockade of venules and arteriole is frequent in sickle cell disease. This is to be expected particularly in the vasa recta supplying the renal papillae where, as compared to the cortex, blood flow is slower, oxygen tension is lower (5) and blood osmolality is higher (4, 6). These factors favor the occurrence of sickling which would further decrease blood flow (7, 8).

Isosthenuria is the most frequent laboratory finding in these patients, but albuminuria of varying degrees and microscopic or gross hematuria are also seen. Initially supernormal discrete renal functions may be found which have been ascribed to increased cardiac output due to anemia (3). In patients surviving into the third or fourth decade progressive loss of function eventually leading to renal insufficiency indistinguishable from that seen in chronic glomerulonephritis is sometimes seen (1).

Features of the nephrotic syndrome have been occasionally observed with sickle cell disease but the full clinical picture appears to occur only very rarely (2). We have therefore thought of interest to record a recently observed case in which a nephrotic-uremic picture occurred in an adult with sickle cell disease.

From the Medical and Laboratory Services, Veterans Administration Hospital, San Juan, Puerto Rico.

Case Report

A 37 year old Negro male was hospitalized at the San Juan Veterans Administration Hospital for the first time in October 25, 1954 complaining of bone pain, fever and jaundice lasting for 10 days. The patient had suffered from similar episodes since the age of 9 years and had been hospitalized at the San Juan City Hospital for treatment of sickle crises. A pre-induction physical examination in February 1952 had revealed no abnormalities; however, repeated examinations of the urine during April and July 1953 showed varying degrees of albuminuria. Blood pressure was 130/70 mm Hg. The patient was accepted in the military service in August 1954, the urinary findings being

diagnosed as "orthostatic albuminaria". A week after induction he developed pain in the right knee, fever, jaundice and leukocytosis. The illness was again diagnosed as sickle cell anemia with crises and it prompted his discharge from the military service. The diagnosis was confirmed during his initial V. A. hospitalization. Hemoglobin ranged around 10 g/100 ml, urinalysis showed 2+ albuminuria and a positive sickling test was obtained. Maximum concentration on Fishberg test was 1.012; phenolsulphthalein excretion was 65% in 2 hours, and paper electrophoresis showed S hemoglobin.

Roentgen examinations of the chest and skull were normal. Cholecystogram showed multiple calculi. The patient was discharged improved after symptomatic treatment and blood transfusions.

During 1955 the patient was hospitalized on four occasions for treatment of crises. During the second of these admissions a cholecystectomy was performed. From 1956 to October 1965 he was hospitalized twenty seven times with similar symptoms, being treated with blood transfusions, analgesics and distilled water infusions. His hemoglobin remained around 10.5 g % and urinalysis revealed varying degrees of albuminuria. During this period of time he developed changes characteristic of sickle cell disease in the ribs and clavicles. Splenomegaly was detected during 1957. This same year the patient was given prednisone 5 mg twice a day, which was continued for 10 months. In 1960 swelling of the deltoid muscles was observed.

On September 8, 1965 the patient was hospitalized with a hemolytic crisis. While in the hospital he developed a pharyngeal inflammation which was treated with penicillin. Throat culture yielded normal flora. He was readmitted on October 12, 1965 with a five-day history of progressive generalized edema. No history of flank pain or hematuria was obtained. Blood pressure was 150/80 mm Hg. He was pale and edematous. No jaundice, hepatosplenomegaly or ascites was detected. Laboratory studies showed the following: Urinalysis, 4+ albumin, numerous WBC in the sediment and a specific gravity of 1.012. Hemoglobin was 5.3g %; hematocrit, 20.6%; RBC, 1,970,000/cu. mm., and WBC, 13,700/cu. mm. Neutrophiles were 70%; lymphocytes, 15%; monocytes, 6%; eosinophiles, 1% and bands, 8%. VDRL microflocculation was non-reactive. The serum creatinine was 5.4 mg per cent; creatinine clearance was 6.7 ml per minute and the blood urea nitrogen (BUN), 44 mg %. Serum proteins were 1.7 g % albumin and 3.3 g % globulin. Urine culture was negative. The urinary albumin was 14 g in 24 hours. PSP excretion was 4% in 2 hours; serum cholesterol, 272-365 mg %. Doubly-refractible bodies were observed in the urinary sediment. Serum electrolytes were as follows: Na, 133 mEq/L; K, 5.9 mEq/L; Cl, 109.5 mEq/L; and Co_2, 15.3 mEq/L. The serum phos-

TABLE I: SELECTED LABORATORY EXAMINATIONS AND BLOOD PRESSURE

	Feb. 1952	July 1953	May 1959	Mar. 1960	Sept. 1965	Oct. 1965	Jan. 1966	Aug. 1966
Urinalysis:								
specific gravity	1016	1010	1017	1010	1006	1012	1010	1008
albumin	Neg	3+	2+	4+	4+	4+	3+	4+
sediment	Normal	Casts, hyaline, few	3-5WBC 2-4RBC	Casts, granular, 3-5	4-8WBC Casts, granular rare	Many WBC	2-4RBC 3-5WBC	30-40RBC 8-10WBC Casts
Urea N (mg %)		9				44	10	130
Creatinine (mg %)						5.4	10	16.6
Albumin, serum (g %)					3.1	1.7	—	2.8
Blood pressure (mm Hg)	130/70	120/68	130/70	130/70	130/86	150/80	176/90	170/110

phorus was 9.1 mg %. Intravenous pyelogram showed no visualization of either kidney. Kidney size could not be determined. Roentgenograms revealed calcification of the spleen and extensive osseous changes in the spine, both iliac bones and the left femur compatible with sickle cell anemia.

Management in the hospital consisted of diuretic therapy with Aldactone® and chlorothiazide and packed red blood cell transfusions. Digoxin was also given upon development of tachycardia and severe shortness of breath. Dextran-70, 6%, in saline, was administered with no apparent effect. While hospitalized the BUN remained around 60 mg %, the hemoglobin about 6.0 g %, the serum creatinine, 9.0 mg %. The blood pressure was usually about 160/90 mm Hg. Upon discharge on December 7, 1965, symptoms were moderately improved and his weight had diminished to 166 lbs. He was followed as an outpatient and continued on diuretic therapy.

On January 7, 1966 he was readmitted because of abdominal pain, nausea and vomiting. He was continued on diuretics, placed on a low protein diet and given packed red cell transfusions. He was discharged on April 20, 1966 his renal status essentially unchanged.

The final admission of this patient was on August 5, 1966 at which time he came in complaining of nausea, vomiting, fever, diarrhea and generalized bone pains. He appeared chronically ill and edematous. Hemoglobin was 4 g %; BUN was 130 mg %; creatinine, 16.6 mg % and blood pressure was 170/110 mm Hg. He improved during the first few weeks of hospitalization with diuretic therapy and low protein diet. However, thereafter he rapidly developed uremic symptoms, congestive heart failure, oliguria and he expired on September 23, 1966.

At necropsy edema of the trunk and extremities was found. The liver was slightly enlarged and soft. The spleen weighed 190 g, being firm and showing many small yellow-brown infarcts. The heart weighed 500 g but showed no gross abnormality. The kidneys were small (combined weight, 110 g) with a finely granular surface. There was marked atrophy of the cortical substance. Petechial hemorrhages were found in the cortex. The renal pyramids were pale and three was obliteration of the vascular striations. No gross abnormalities of the renal arteries or veins were found. The testes were atrophic.

The vertebral bone marrow showed erythroid hyperplasia. In the spleen, replacement of the malpighian bodies with siderotic nodules, old and recent hemorrhages, and hemosiderin-laden macrophages were seen. Prussian blue reaction for iron was strongly positive. The liver and pancreas showed considerable deposition of hemosiderin. Hypertrophy of the myocardial fibers was noted on sections from the left ventricle.

Both kidneys showed hypercellularity of the glomerular epithelium and thickening of the basement membrane (Fig. 1). In other glomeruli this

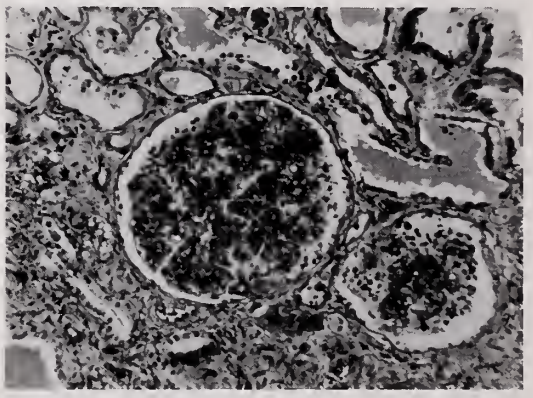


Fig. 1: Hyperplastic glomerulonephritis. Note proliferation of endothelium and epithelium of glomerular capillaries and thickening of basement membrane (H&E stain, X175).

process had progressed into various degrees of sclerosis and hyalinization (Fig. 2). In some, the glomerular capillaries presented a lobular pattern. PAS stain showed the thickening of the basement membranes to better advantage (Fig. 3). There were marked atrophic changes of the tubules in large areas interspersed with other lobular areas where they were hypertrophied and dilated. The interstitial stroma in the atrophic areas showed predominantly lymphocytic infiltration and fibroblastic proliferation. Many Henle's loops and distal collecting ducts showed epithelial necrosis. The distal and collecting tubules contained granular and cellular casts and pus cells. The renal artery branches and arterioles showed hyperplastic sclerosis. Neither venous thrombosis nor sickling was observed within the renal vasculature.

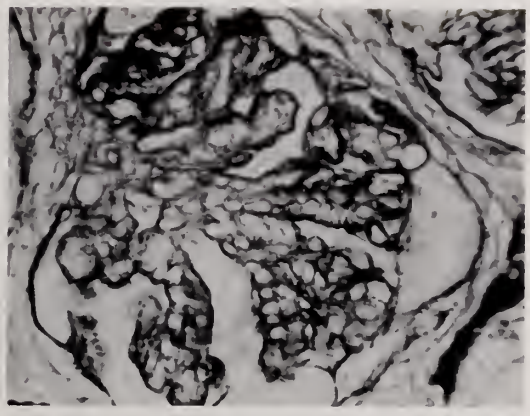


Fig. 2: Photomicrograph shows sclerotic hyalinized glomeruli in the center and atrophic tubules in the field (H&E stain, X100).



Fig. 3: Glomerulus exhibiting thickening of the basement membrane and adhesions to the capsular wall of the glomerulus (PAS stain, X1200).

Discussion

Our patient exhibited most of the classical features of sickle cell disease. In addition to the typical hematologic findings, characteristic complications of gallstones, cardiac hypertrophy, splenic and osseous lesions were observed. This patient's life span was longer than is usually observed in the homozygous disease (9), but not beyond that seen in a significant number of patients in some recent series (10).

The urinary abnormalities first observed in this patient in 1953 consisting of hyposthenuria, variable amounts of albuminuria and occasional formed elements in the sediment are the usual findings in sickle cell anemia. His blood pressure remainded normal throughout the following 12 years. Unfortunately, further evaluation of renal function was not carried out prior to the appearance of a nephrotic syndrome in 1965. This acute renal picture became manifest a few weeks after the patient suffered an acute pharyngitis. Although a streptococcus was not isolated on the single culture obtained, this does not rule out infection with this organism. The subsequent course was a progressive one with the development of uremia and hypertension and death in about one year. The predominant histopathologic lesion found was chronic glomerulonephritis.

The histopathological findings in previously recorded cases in which the coincidence of nephrotic syndrome and sikle cell disease has occurred have not been uniform. The patient described by Berman and Tublin (11) showed pyelonephritis on renal biopsy. Glomerular congestion, fibrosis and "suggestive" thickening of the basement membrane were described by Sweeney (3) in 2 cases. In Wilson's case the characteristic lesions of disseminated lupus erythematosus were found (12). Berman and Schreiner (13) in a review of their experience with nephrotic syndrome, list 2 cases of sickle cell anemia, one showing focal glomerular lesions which were interpreted as hyaline thrombi, advanced nephrosclerosis and parenchymal damage and

the other similar but less advanced changes.

Sweeney (3) has suggested that a nephrotic syndrome may develop in cases of sickle cell anemia thru a mechanism similar to what has been postulated to explain the renal picture in constrictive pericarditis (14, 15) and renal vein thrombosis (16, 17). In these conditions a glomerular lesion indistinguishable from membranous glomerulonephritis has been attributed to vascular stasis and ischemia resulting in glomerular capillary damage and intracellular molecular change providing the antigen for the occurrence of an antigen-antibody reaction which in turn results in the development of glomerulonephritis. The finding of bilateral glomerular lesions and the demonstration of deposition of antiglobulin in the glomeruli in a case of unilateral renal vein thrombosis (17), seem to favor this mechanism.

Whether an autoimmune process operates in some cases of sickle cell anemia remains to be established. The infrequency of the occurrence of a combination of these two conditions makes it unlikely. In our patient, as in Sweeny's (3), it seems more likely that infection with a hemolytic streptococcus was the case of the predominant renal lesion, which became superimposed on previous renal damage related to sickle cell disease. Serial determinations of antistreptolysin and complement might have given support to this supposition but unfortunately were not done.

A possible therapeutic approach in this type of case is the administration of corticosteroids or corticotropin. This has been tried with moderate success by Sweeney (3), but Berman (11) observed no beneficial effects. This was not employed in our patient. Instead, and on the assumption that vascular stasis might be a factor in the development of the renal lesion (18), we performed an acute experiment using 6% dextran-70 intravenously but obtained no positive results. Other studies have demonstrated no benefit from this therapy on the manifestations of drepanocytosis (19). Otherwise it would seem best to follow the same princpiles of management as in other renal diseases.

Summary

The case is described of a 37 yr. old male with homozygous sickle cell disease who developed a nephrotic-uremic picture following an acute pharyngitis. Urinary abnormalities including hyposthenuria and albuminuria had been present for 13 years before and have been attributed to sickle cell disease. The predominant renal anatomopathological findings were characteristic of chronic glomerulonephritis and seem to have been due to a streptococcal pharyngitis occurring one year before death.

Resumen

Se trata de un varón de 37 años con drepanocitemia, quien desarrolló un cuadro nefrótico y luego uremico después de una faringitis aguda. Se habían observado anormalidades urinarias incluyendo hipostenuria y albuminuria 13 años antes, las cuales se atribuyen a la drepanocitemia. La lesión renal predominante se consideró característica de glomerulonefritis crónica. Se discute brevemente la patogénesis de lesiones renales en drepanocitemia.

Acknowledgement

The autopsy material was reviewed by Dr. Bela Halpert of the Armed Forces Institutes of Pathology (accesion No. 1245567), who concurred with our findings.

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ACTUALIDADES MEDICAS

Heart Transplant Coming Soon, Surgeon Says

"We think the way is clear for trial of human heart transplantation," says surgeon Norman E. Shumway, M.D., in an interview in the Medical News section of the Nov. 20 Journal of the American Medical Association.

One person's heart will be transplanted to another's body as soon as a suitable donor and recipient can be found, said Dr. Shumway, who is head of the Division of Cardiovascular Surgery at Stanford Medical Center, Palo Alto, Calif.

"We have achieved a degree of experience with (animal) heart transplantation in the laboratory which makes us confident we can take appropriate care of the patient with a cardiac transplant," Dr. Shumway told JAMA's Medical News section.

The most likely candidate to receive a heart would be a patient whose own heart cannot be restored to normal pulse when taken off a heart-lung machine during open-heart surgery.

Other possible recipients being considered at Stanford are children born with heart defects for which there is no corrective surgery or treatment. An infant with tricuspid atresia (the absence or closure of one of the heart's major valves) would be a possible recipient, Dr. Shumway said.

The ideal heart donor would be a relatively young person dying of causes unconnected with heart disease.

Thus far, the ideal donor and ideal recipient have not coincided at the Stanford Medical Center, although patients of both types have been treated there recently.

Dr. Shumway stressed that animal experimentation should and will continue, but "we are nonetheless at the threshold of (human) application" of heart transplant knowledge.

Experimental evidence shows that if the heart can be removed from the donor within a half-hour after death, it can be resuscitated without suffering damage from oxygen lack. This time span can be lengthened somewhat by immersing the heart in cold salt-water solution.

The important factor is not so much the overall time of oxygen lack, but the period of oxygen shortage at body temperature.

"This is what is damaging to he heart, the period of normal temperature during which there isn't any circulation in the coronary arteries," Dr. Shumway said.

It may be possible to maintain a heart for short periods by cross-circulation with a third patient or with a heart-lung machine, he said.

"But at the moment, we are depending upon the coincident situation in which the donor and recipient are immediately available."

This means that as long as heart transplantation is confined to emergency situations, its use will depend upon the chance

availability of a suitable donor heart at the time of need.

Heart transplantation thus is not likely to achieve widespread use until (1) methods are found for preserving the heart or (2) further experience allows surgeons to transplant hearts as elective surgery when donors are available.

The surgical technique of transplantation has been thoroughly worked out in the laboratory, and technical difficulties are not expected in the first human transplant, the Journal article said.

In fact, transplantation in the human probably will be less difficult than in the dog, the article said, because a dog's aorta is unusually fragile.

Immune reactions, the body's defense against foreign bodies and a major problem of any organ transplant, is expected to be approximately the same for a transplanted heart as for transplanted kidneys. However, laboratory experience suggests that a heart-transplant patient might not be able to tolerate the high drug dosages sometimes administered to suppress immune reactions.

This has led to an extensive search for guidelines as to what kind of hearts a patient's body might "reject." In turn, this has contributed knowledge about how little drug dosage can be administered for the maximum amount of immunity suppression.[1]

"Dr. Shumway does not anticipate social or legal difficulties in cardiac transplantation, although these may restrict use of the technique in some areas," the Journal report said.

There are subjective attitudes about the heart that don't apply to transplanted kidneys or livers, Dr. Shumway pointed out.

"There are a great many emotional problems involving the heart, but the public is, in fact, adopting a more liberal attitude toward organ transplantation," he said.

The period between death and heart removal is the time when irreversible brain damage sets in.

"Therefore, removal of the heart cannot be objected to on the grounds that if it can be resuscitated outside the donor's body there existed the possibility that the donor himself could have been revived," the Journal report said.

Said Dr. Shumway: "What is needed is to acquaint the public with the necessity of using relatively fresh human tissue for transplantation.

"And I believe that people are becoming more interested in the possibilities of heart transplantation. If they surmise that it is possible, they soon will demand that it be done."

Normal Conversion of Chemical to Mechanical Energy in Cardiac Failure

Scientists of the Public Health Service's National Heart Institute report that the failing heart converts chemical energy to mechanical work at least as efficiently as does the normal heart. Previously, the fundamental biochemical defect in heart failure had been attributed by many to a defect in energy utilization. This defect is now thought to be either in the contractile proteins actin and myosin, which are the basic elements of contraction of the heart muscle fibril, or in the process of excitation-contraction coupling, by which the heart muscle is activated. In excitation-contrac-

tion coupling, calcium within the muscle is released and in turn causes a release of energy for the heart's contractions. This energy release causes the muscle to contract.

In order to determine whether there was any defect in energy transfer in the failing heart, Dr. Peter E. Pool and co-workers at National Heart Institute studied the direct conversion of chemical energy to mechanical work in right ventricular papillary muscles from normal cats and cats with experimental right ventricular failure.

The papillary muscles were treated to prevent the production of ATP from the metabolism of foodstuffs. The muscles were then stimulated to perform work by pulling against a load, and the amount of work was measured. They were then frozen and analyzed to determine the amount of ATP present. This gave a measurement of the amount of energy burned. The investigators found that failing heart muscles and normal heart muscles used the same amount of ATP energy per unit of work. This indicates that the failing heart converts chemical energy to mechanical work as efficiently as the normal heart.

Since the biochemical defect in heart failure is not in energy utilization, the National Heart Institute investigators postulate that the defect must be either in the contractile proteins or in excitation-contraction coupling.

These results were reported at the 40th Scientific Sessions of the American Heart Association in San Francisco by Drs. Peter E. Pool, Brian M. Chandler, James F. Spann, Edmund H. Sonnenblick and Eugene Braunwald of the Public Health Service's National Heart Institute.

Divorce Statistics: The Seven-Year Itch?

This report* is an analytical study of the 1963 divorce and annulment statistics for the United States. Detailed data on divorces and annulments classified by demographic and legal variables are limited to the 22 States that participated in 1963 in the divorce-registration area (DRA).

The divorce rate for the United States is higher than that for any other nation that reports this information to the Statistical Office of the United Nations.

The divorce rate was below the national average in 25 States, most of which are located on the Atlantic Coast and in the northern part of the North Central Region.

It is estimated that only about 1 divorce in 20 is granted annually to persons who move to another State temporarily for the sole purpose of getting divorced.

Data received from 22 States participating in the divorce-registration area indicate that young persons and persons who were remarried have an above-average likelihood of divorce. It was also estimated that the likelihood of divorce declines with increasing duration of marriage.

The median duration of marriage at time of decree was 7.5 years in 1963. There are indications that the duration has increased slightly during the 1954-63 decade.

Couples divorced in the United States reported an estimated 583,000 children under 18 years of age. This represents 1.36 children per decree, or 8.5 per 1,000 children in the Nation. The number of chil-

Reproduced from Vital and Health Statistics, Public Health Service Publication No. 1000-Series 21-No. 13.

dren increased much more rapidly than the number of decrees: in 1953 there were only 0.85 children per decree.

The great majority of divorce decrees were granted on grounds of cruelty, desertion, nonsupport, and indignities. About 20,000 decrees were granted on two grounds or more—the most widely used combination was cruelty and nonsupport.

CARTA

LA NUTRICION Y LOS PARASITOS INTESTINALES.

Numerosos estudios clínicos y experimentales indican que existe una estrecha interrelación entre los procesos infecciosos que por un lado deterioran el estado nutricional y la desnutrición que, por el otro, constituye un factor agravante durante las enfermedades infecciosas. En Puerto Rico y, con más intensidad aún, en varios países latino-americanos, las infecciones intestinales, las parasitosis, la mortalidad infantil y la desnutrición están íntimamente relacionadas.

En nuestro país, se han realizado grandes logros en el control de las infecciones intestinales (Diarrea-Enteritis) reduciendo la mortalidad general por esta condición de 22% en 1940 a solamente 6% en 1966. También se ha reducido grandemente la mortalidad infantil de 127.3 muertes por cada 1000 nacidos vivos en 1936 a 37.0 en 1966. Sin embargo, la prevalencia de los parásitos intestinales más comunes (Trichuris, Ascaris, Uncinarias) ha variado muy poco en los últimos 20 años.

Si consideramos que la parasitosis intestinal constituye hoy día la afección enteral que más comúnmente contribuye a la desnutrición de nuestros niños, siendo causa frecuente de anemias severas, hipoproteinemia, desnutrición calórica e hipovitaminosis múltiples, es sumamente necesario que las personas que laboran en el campo de la salud se preocupen por este problema. No debemos darle tregua a estas enfermedades que constantemente tronchan esperanzas y destruyen vidas jóvenes en nuestra comunidad.

La tarea es compleja y requiere la participación de técnicos en los campos de nutrición, saneamiento, educación y otros. En Puerto Rico, haciendo uso de estos recursos en forma coordinada se podría lograr mucho más de lo que se ha alcanzado hasta el presente; pues, a mi entender, el problema de parasitosis intestinal en nuestro país solamente podrá solucionarse cuando se empleen a capacidad y en forma integrada los esfuerzos y conocimientos del médico, la nutricionista, el oficial de saneamiento, el educador, el epidemiólogo, el parasitólogo, la enfermera, el sociólogo y otros técnicos profesionales con que cuenta hoy día nuestro gobierno, la Universidad de Puerto Rico y la comunidad.

En nuestro medio, el peor enemigo resulta ser la reinfección continua que ocurre en el ámbito familiar y para combatir la cual, los medios actuales son poco efectivos. Los tratamientos médicos contra Trichuris, Ascaris y Uncinarias son 100% efectivos cuando se administran a dosis adecuadas y en condiciones óptimas de saneamiento e higiene. Sin embargo, la reinfección en el medio ambiente familiar de nuestra gente humilde es tan grande que es urgentemente necesario el desarrollar o descubrir medidas sanitarias, educativas, y otras mucho más efectivas que las utilizadas actualmente.

No tengo la menor duda que del esfuerzo unido de todos surgiría inevitablemente la solución práctica y efectiva para este serio problema que pretende persistir por muchos años más. Erradiquemos estos parásitos y habremos dado un paso gigante hacia la nutrición y salud óptima de nuestro pueblo.

Urge formar una comisión destinada a elaborar un plan de aplicación estatal.

Nelson A. Fernández López, M.D.

NOTICIAS

Locales

Reuniones

6-10 feb.—Convención Anual de la Sección de Pediatría de la Asociación Médica de Puerto Rico.

23-24 feb.—Convención de la Sociedad de Médicos Graduados de México.

WESTERN HEMISPHERE NUTRITION CONGRESS II

The second Western Hemisphere Nutrition Congress will be held in San Juan, Puerto Rico, August 26-29, 1968. The Congress has been organized by the American Institute of Nutrition and the American Medical Association's Council of Foods and Nutrition in cooperation with the Nutrition Society of Canada and the Latin American Nutrition Society.

The four-day program consists of fourteen sessions of nearly 100 presentations. The multidisciplinary format of the 1965 Congress which provided wide coverage of significant developments has been retained. Emphasis is given to research and program developments in Latin America. The sessions, in addition to the opening and closing plenary programs are:

Nutrition and Human Development
Food Production, Distribution and Economics
Recent Advances in Nutrition
Recent Advances in Development and Applied Food Technology
Research Forum (submitted abstracts)
Vitamin A Metabolism and Deficiency
Nutrition Research and Applied Nutrition Programs in the Caribbean
Iron Deficiency Anemia, Diagnosis, Prevalence, and Treatment
Applied Nutrition Programs in the Americas

Scientists are invited to submit abstracts for presentation during the Research Forum. The Forum will consists of four concurrent sessions dealing with atherosclerosis, protein-calorie malnutrition and nutrition anemias, trace mineral and vitamin metabolism, and food science. Three-hundred world abstracts should be sent to Dr. William N. Pearson, Division of Nutrition, School of Medicine, Vanderbilt University, Nashville, Tennessee 37203. The abstracts must be received prior to March 1, 1968 to be included in the program.

Registration for the Congress which will be held at the San Jerónimo Hilton Hotel is $30.00. Rooms for participants have been reserved at nearby hotels. The A.M.A. will coordinate hotel reservations. For program, registration and hotel information, contact the Council on Foods and Nutrition, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

Registration for local students and paramedical personnel will be $10.00—banquet and proceedings not included.

NEW BOOKS

Other books received by the University of Puerto Rico School of Medicine and School of Dentistry.

Anthropology:

1. Ciba Foundation. Symposium on caste and race; comparative approaches. Boston, Little, 1967.

Biology:

1. Riley, Ralph, ed. Chromosome manipulations and plant genetics. New York, Plenum Press, 1966. QK981.

2. Seliger, Howard H. Light: physical and biological action. New York, Academic Press, 1965. QH651.

3. Sturtevant, Alfred Henry. A history of genetics. New York, Harper & Row, 1965. QH431.

4. Williams, George Christopher. Adaptation and natural selection. Princeton, N. J., Princeton University Press, 1966. QH546.

Language:

1. Buttress, F. A. World list of abbreviations. 3rd ed. London, Hill, 1966. AS8.

2. Cassell's new Latin dictionary. Latin-English, English-Latin by D. P .Simpson. New York, Funk & Wagnalls, 1959. PA2365.

3. Craddock, F. W. Dental writing, notes on the anatomy and pathology of English composition for dentists, Dunedin, University of Otago Press, 1962. Z253.

4. Velázquez de la Cadena, Mariano, comp. Dictionary of the Spanish and English language. New York, Appleton, 1967. PC4640.

Pharmacology:

1. Abbott Laboratories. Erythromycin, a review of its properties and clinical status. North Chicago, Illinois, 1966. QV350.

2. Nuñez Meléndez, Esteban. Farmacognosia moderna; materia médica de origen vegetal y animal. Madrid, Imprenta S. M., 1967. QV752.

3. Smith, M. J. H., ed. The salicylates. New York, Interscience Publishers, 1966. QV95.

4. Usdin, Earl. Psychotropic drugs and related compounds. Wash., D. C., National Clearinghouse for Mental Health Information, 1967. QV77.

5. Workshop on Antidepressant Drugs, NON/MAO Inhibitors. Proceedings. Bethesda, Maryland, National Institute of Mental Health, 1966. QV77.

6. Falconer, Mary W. Current drug handbook 1966-68. Phila,, Saunders, 1966. QV55.

Chemistry and Biochemistry:

1. American Medical Association. Let's talk about food, answers to your questions about food and nutrition. Chicago, 1967. QU145.

2. Ciba Foundation Study Group No. 24, London, 1965. Histones: their role in the transfer of genetic information. Boston, Little, Brown, 1966. QU55.

3. Ciba Foundation Study Group No. 28. Thiamine deficiency: Biochemical lesions and their clinical significance. Boston, Little, Brown and Co., 1967. WD120.

4. Douglas, Bodie E. Concepts and models of inorganic chemistry. Ist ed. New York, Blaisdell Pub. Co., 1965. QD475.

5. Dutton, Geoffrey J., ed. Glucuronic acid. New York, Academic Press, 1966. QU83.

6. Frankel, Max. Tables for identification of organic compounds. 2d ed. Cleveland, Chemical Rubber Co., 1964. QD291.

7. Heinz (H.J.) Company. Nutrición humana. Washington, Organización Panamericana de la Salud, 1966. QU145.

8. Hodges, Robert E. Effects of carbohydrates on lipid metabolism of man, a review of the literature, 1935-1966. Chicago, Cereal Institute, 1967. QU85.

9. Hsia, I-jung. Inborn errors of metabolism. 2d ed. Chicago, Year Book Medical Publishers. 1966. QU120.

10. Jelliffe. Derrick B. The assessment of the nutritional status of the community (with special reference to field surveys in developing regions of the world) Geneva, World Health Organization, 1966. QU146.

11. Leblond, Charles P. The use of radioautography in investigating protein synthesis. N. Y., Academic Press, 1965. SERIAL.

12. Lehninger, Albert L. Bioenergetics: the molecular basis of biological energy transformations. N. Y., W. A. Benjamín, 1965. QU125.

13. Méjico. Instituto Nacional de la Nutrición. Veinte años de enseñanza e investigación, 1946-1965. Méjico, 1966. QU145.

14. National Dairy Council. Newer knowledge of cheese. 2d ed. Chicago, 1967. QU145.

15. National Research Council. Committee on Biological Chemistry. Specifications and criteria for biochemical compounds. Wash., National Academy of Sciences, National Research Council, 1960. SERIAL.

16. Patton, Alva Rae. Biochemical energetics and kinetics. Phila., Saunders, 1965. QU125.

17. Symposium on Progress in Biochemistry and Therapeutics, 3d, New York, 1966. Enzymes in mental health. Phila., Lippincott, 1966. QU135.

18. U. S. National Library of Medicine. The nucleic acids: an annotated bibliography. Wash., U. S. Govt. Print. Office, 1966. ZQU55.

Gynecology and Obstetrics:

1. Beck, Alfred Charles. Beck's obstetrical practice. 8th ed. Baltimore, Williams and Wilkins, 1966. WQ100.

2. Calderone, Mary Steichen, ed. Manual of contraceptive practice. Baltimore, Williams & Wilkins, 1964. WP630.

3. Ciba Foundation Study Group No. 26. Effects

of external stimuli on reproduction. Boston, Little, Brown, and Co., 1967. WQ205.

4. Crawford, J. S. Principles and practice of obstetric anaesthesia. 2d ed. Philadelphia, F. A. Davis, 1965. WO450.

5. Eastman, Nicholson, Joseph. Williams Obstetrics. 13th ed. New York, Appleton-Century-Crofts, 1966. WQ100.

6. Juret, Paul. Endocrine surgery in human cancers. 2d ed. Springfield, Ill., Thomas, 1966. WP870.

Skeletal System:

1. Conference on Facial Disfigurement. Facial disfigurement, a rehabilitation problem. A conference... March 21-22, 1963, New York. Wash., Vocational Rehabilitation Administration, 1966. WE705.

2. Conference on the Relationship of Mychoplasma to Rheumatoid Arthritis and Related Diseases. Proceedings. Bethesda, Maryland, U. S. National Institute of Arthritis and Metabolic Diseases, 1966. WE346.

3. Goff, Charles Weer. Traumatic cervical syndrome and whiplash. 1st ed. Philadelphia, Lippincott, 1964. WE708.

4. Wise, Robert Alexander. Surgery of the head and neck. 2d ed. Chicago, Year Book Medical Publishers, 1962. WE705.

Serials:

Advances in enzyme regulation. v.4, 1966.
Advances in internal medicine. v.13, 1967.
Brookhaven Lectures Series, no. 55. Early history of associated universities and Brookhaven National Laboratory. Springfield, 1966.
Brookhaven symposia in biology, no. 19. Energy conversion by the photosynthetic apparatus. June 6-9, 1966. Pub. 1967.
Clinical Anesthesia. No. 3, 1966.
Clinical obstetrics and gynecology. v.10, no. 1, March, 1967.
Clinical obstetrics and gynecology. v.10, no. 2, June, 1967.
Clinical orthopaedics and related research. no. 49 1966.
Clinical orthopaedics and related research. no. 50; 51, 1967.
Cumulative index to nursing literature. v.11, 1966.
Dental clinics of North America. March, July, 1967.
Index to dental literature. v.36, 1966.
Medical clinics of North America. v.51, No. 2-4, 1967.
Modern trends in dermatology. v.3, 1966.
New drugs. 1967 edition.
Pediatric clinics of North America. v.14, No. 2-3, 1967.
Perspectives in virology. v.4, 1965.
Progress of medical parasitology in Japan. v.3, 1966.
Radiologic clinics of North America. v.5, No. 1, 1967.
Surgical clinics of North America. v.47, No. 1-4, 1967.
Transactions of the Association of Life Insurance Medical Directors of America. v.50, 1966.
U. S. National Cancer Institute Monograph 23, 1966; 24, 1967.
Yearbook of cancer. 1966-1967.
Yearbook of dentistry. 1966-1967.
Yearbook of drug therapy. 1966-1967.
Yearbook of ear, nose and throat. 1966-1967.
Yearbook of neurology, psychiatry, and neurosurgery. 1966-1967.
Yearbook of nuclear medicine. v.2, 1967.
Yearbook of ophthalmology. 1966-1967.
Yearbook of pediatrics. 1966-1967.
Yearbook of radiology. 1966-1967.
Yearbook of urology. 1966-1967.

Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Feb. 28, Mar. 2— Hypertensive Cardiovascular Diseases: Mechanism and Treatment. Clinical Research Institute of Montreal,, Montreal, P.Q., Canada.

Mar. 14-16—The Clinical Selection of Patients for Cardiac Surgery. Mayo Graduate School of Medicine (University of Minnesota) and Mayo Clinic, Rochester, Minn.

Mar. 18-22—Psychiatry and the Internist. Albany Medical College of Union University, Albany, N. Y.

Mar. 28-30—Current Concepts in Physiology of Respiration, Circulation and Electrolyte Metabolism, co-sponsored with the American Physiological Society, to be held at the Somerset Hotel, Boston, Mass.

Apr. 22-26—Clinical Endocrinology — Recent Advances in Diagnosis and Treatment. Mayo Graduate School of Medicine (University of Minnesota) and Mayo Clinic, Rochester, Minn.

May 12-15—Frontiers in Gastroenterology. University of Pennsylvania School of Medicine, to be held at the Bellevue Stratford Hotel, Philadelphia, Pa.

OTHER MEETINGS

Apr. 4-6—Third National Conference on Health Education of the Public, to be held at Pick-Congress Hotel, Chicago, Ill. Sponsored by the Department of Socio-Economic Activities of the American Medical Association.

AMERICAN MEDICAL ASSOCIATION MEETINGS

Feb.8-10—Board of Trustees, Chicago, Ill., AMA Headquarters.

Feb. 8-13—Congress on Medical Education, Chicago, Ill., Palmer House

Feb. 9-10—Residency Review Committee in Internal Medicine, DGME, Chicago, Ill., Drake Hotel, 9:00 a.m.

Feb. 10.—Council on Medical Education, Chicago, Ill., Palmer House.

Feb. 11-12—Annual Congress on Medical Education, Chicago, Ill., Palmer House, Grand Ballroom.

Feb. 22-23—Committee on Medicine and Religion Chicago, Ill., Feb. 22, Drake Hotel; Feb. 23, AMA Headquarters.

Mar. 2-3—Conference Committee on Graduate Training in Surgery, DGME, Chicago, Ill., Drake Hotel, 8:30 a.m.

Mar. 4—Residency Review Committee for Neurological Surgery, Des Plaines, Ill., O'Hare Inn, 9:00 a.m.

Mar. 8-10—Council on Medical Education, Denver, Colo., Brown Palace Hotel.

Mar. 11-15—New Medical Executives School, Chicago, Ill., AMA Headquarters.

Mar. 14—Council on Mental Health, Chicago, Ill., Drake Hotel.

Mar. 15-16—Council on Mental Health 14th Annual Conference of State Mental Health Representatives, Chicago, Ill., Drake Hotel.

Mar. 22-23—Second National Congress on the Socio-Economics of Health Care, DSEA, Chicago, Ill., Palmer House.

Mar. 27—Council on Rural Health, DHE, Seattle, Wash., Olympic Hotel, 2:00 - 10:00 p.m

Mar. 28—Meeting for State Medical Association Rural Health Committee Chairmen, DHE, Seattle, Wash., Olympic Hotel, 6:00 - 10:00 p.m.

Mar. 28—Seminar for Extension Specialists in Health and Related Fields, DHE, Seattle, Wash., Olympic Hotel, 9:00 a.m. - 4:30 p.m.

Mar. 29-30—21st National Conference on Rural Health, DHE, Seattle, Wash., Olympic Hotel, Mar. 29, 9:00 a.m.-5:00 p.m.; Mar. 30, 9:00 a.m. - 12:00 noon.

Mar. 30—Residency Review Committee for Anesthesiology, DME, Scottsdale, Ariz., Valley-Ho Hotel, 9:00 a.m. - 5:00 p.m.

Mar. 30-31—Second National Congress on Medical Ethics, Chicago, Ill., Drake Hotel.

Apr. 4-6—Board of Trustees, Chicago, Ill., AMA Headquarters.

INACTIVATED MEASLES VACCINE*
Discontinuance of Use

In the past the Committee on Control of Infectious Diseases has listed among schedules recommended for measles immunization several which included inactivated (killed) measles virus vaccine.

Unusual local and systemic reactions occurring when recipients of inactivated vaccine later encountered natural measles or received live attenuated measles virus vaccine have been documented in reports from the U.S.A. and elsewhere. These reactions have taken two forms:

1. Exposure to measles has resulted in overt illness with an atypical rash (beginning on the feet and extending upward, concentrated on the lower extremities, with petechial, vesicular and urticarial components), pneumonia, edema, high fever and toxicity;
2. Administration of live vaccine has induced a reaction at the injection site with erythema, heat, tenderness, swelling and a localized vesicular or hemorrhagic lesion accom-

* *Published with permission of the American Academy of Pediatrics.*

panied systemically by fever, malaise and regional lymphadenopathy.

All the variables which may affect the magnitude and incidence of these disturbing responses are not yet known. In one town, 11 of 66 children at risk developed the atypical illness when exposed to natural measles 4 years after administration of inactivated vaccine. In a different setting, 9 of 31 children displayed local reactions when given vaccine one year after a course of inactivated antigen. Reactions of this sort have not been observed with live, attenuated virus vaccine or natural measles unless prior sensitization had been induced by the inactivated vaccine. Although the pathogenesis of these reactions has not been fully elucidated, their severity and frequency and the likelihood that less overt, unrecognized forms may occur, justify a reconsideration of the use of this vaccine at this time.

The Committee therefore recommends that:

1. Inactivated measles vaccine be deleted from all schedules of immunization.
2. Live, attenuated virus vaccine be given as soon as possible to all children who may have received only inactivated vaccine previously and their parents be cautioned of possible local and systemic reactions which may occur.
3. Children with underlying illnesses or receiving forms of therapy which contraindicate the use of live vacccines be given immune globulin (human) for protection on exposure to measles. Special attention should be directed to the prompt immunization of the siblings and close contacts of such children with live attenuated vaccine in order to reduce their opportunity for contact with natural disease.

AMA ADOPTS EXPANDED STATEMENT OF PURPOSE

Broad initiative in advancing health care for everyone is detailed in an expanded statement of purposes and responsabilities of the American Medical Association adopted by its House of Delegates and disseminated to all AMA members.

The 11-point document greatly enlarges upon the previous statement of AMA purposes. It puts the skills and resources of the world's largest medical organization behind a continuing effort to stimulate progress in all aspects of health care in America.

The statement declares that it is the responsibility of the AMA, as the representative of the American medical profession, to continue to foster the advancement of medical science and the health of the American people and to discharge that responsibility through the following means:

1. By encouraging the advancement of medical knowledge, skills, techniques and drugs; and by maintaining the highest standards of practice and health care.

2. By creating incentives to attract increasing numbers of capable people into medicine and the other health-care professions.

3. By advancing and expanding the education of physicians and other groups in the health-care field.

4. By motivating skilled physicians who have the art of teaching to apply themselves to developing new generations of excellent practitioners.

5. By fostering programs that will encourage medical and health personnel to serve voluntarily in the areas of need for medical care.

6. By developing techniques and pratices that will moderate the costs of good medical and health care.

7. By seeking out and fostering means of making all health care facilities—physicians' offices, hospitals, laboratories, clinics and others—as efficient and economical as good medical practice and attention to human values will permit.

8. By combining the utilization of the latest knowledge for prevention and treatment with the vital healing force of the physician's personal knowledge of and devotion to his patient.

9. By maintaining the impetus of dedicated men and women in providing excellent health care by preserving the incentives and effectiveness of unshackled medical practice.

10. By maintaining the highest level of ethics and professional standards among all members of the medical profession.

11. By providing leadership and guidance to the medical profession of the world in meeting the health needs of changing populations.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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The drug has no significant uricosuric action but is of value only in the treatment of acute gouty arthritis.
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Warning: Tandearil is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with great caution in the first trimester of pregnancy.
Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately fever, sore throat, or mouth lesions (symptom of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make regular blood counts. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.
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oxyphenbutazone

olding dietary salt, reduction in dosage or use f diuretics. In elderly patients and in those ith hypertension the drug should be discon- nued with the appearance of edema. The rug has been associated with peptic ulcer nd may reactivate a latent peptic ulcer. The atient should be instructed to take doses im- ediately after meals or with milk to minimize astric upset. Mild drug rashes frequently ubside with reduction of dosage. However, ash accompanied by fever or other systemic eactions usually requires withholding medica- on. Purpuric rash has also been reported. granulocytosis or a generalized allergic reac- on similar to a serum sickness syndrome may ccur and require permanent withdrawal of nedication. Stomatitis, salivary gland enlarge- nent, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. It is usually unnecessary to exceed 4 tablets daily. A trial period of 1 week is adequate to determine response; in the absence of a favorable response, discontinue. Maintenance: An effective level is often achieved with 1 or 2 tablets daily, do not exceed 4 daily. 6562-VI(B)R2

For complete details, please see full prescribing information.

Geigy

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

TA-5806

Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

UNA PINTA DE SANGRE NO PROPORCIONA MAS HIERRO

QUE UNA AMPULA DE 5 cc. DE



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

LAKESIDE

PRODUCTOS PARA PACIENTES QUE UD. VE A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.



when abnormal fragility and permeability threaten

protect the body's 60,000 miles of capillaries

with

duo-CVP®

Duo-C.V.P. proves helpful when abnormal capillary permeability and fragility are factors in bleeding in such conditions as habitual abortion, threatened abortion, nonthrombocytopenic purpura, and gingivitis. In a recent study duo-C.V.P. was also found of significant value in strengthening placental capillaries of normal women against passage of fetal erythrocytes into the maternal circulation.*

Duo-C.V.P. is believed to act by decreasing abnormal permeability and fragility of capillaries, thereby reducing bleeding or diapedesis from these vessels.

Each duo-C.V.P. capsule provides: Citrus Bioflavonoid Compound 200 mg., Ascorbic Acid (vitamin C) 200 mg. Usual dosage is 1 capsule 2 or 3 times daily.

and where vitamin K is also indicated...

duo-CVP with vitamin K

Each capsule provides: Citrus Bioflavonoid Compound 200 mg., Ascorbic Acid (vitamin C) 200 mg., Menadione (vitamin K) 1 mg. Usual dosage is 1 capsule daily. **Precaution:** Use with caution during pregnancy, as vitamin K involves the possible hazard of kernicterus and hyperbilirubinemia in the newborn.

*Clayton, E. M. et al.: Obstet. & Gynec. 29:382, 1967.

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Help can be weeks away
for a painful shoulder.
Except with Butazolidin® alka.
If it doesn't work in a week,
forget it.

t don't forget this about Butazolidin alka

ntraindications: Edema; danger of cardiac compensation; history or symptoms of pep- ulcer; renal, hepatic or cardiac damage; tory of drug allergy; history of blood dys- sia. The drug should not be given when the tient is senile or when other potent drugs are en concurrently. Large doses of Butazolidin a are contraindicated in glaucoma.

rning: If coumarin-type anticoagulants are en simultaneously, watch for excessive in- ease in prothrombin time. Instances of vere bleeding have occurred. Pyrazole com- unds may potentiate the pharmacologic tion of sulfonylurea, sulfonamide-type ents and insulin. Carefully observe patients eiving such therapy. Use with great caution he first trimester of pregnancy.

ecautions: Before prescribing, carefully ect patients, avoiding those responsive to tine measures as well as contraindicated ients. Obtain a detailed history and a com- te physical and laboratory examination, in- ding a blood count. The patient should not ceed recommended dosage, should be sely supervised and should be warned to continue the drug and report immediately if er, sore throat, or mouth lesions (symptoms blood dyscrasia); sudden weight gain (water ention); skin reactions; black or tarry stools other evidence of intestinal hemorrhage cur. Make regular blood counts. Discontinue drug immediately and institute counter- asures if the white count changes signifi- ntly, granulocytes decrease, or immature ms appear. Use greater care in the elderly d in hypertensives.

verse Reactions: The most common are sea, edema and drug rash. Swelling of the kles or face may be minimized by withhold- dietary salt, reduction in dosage or use of iuretics. In elderly patients and in those with pertension the drug should be discontinued h the appearance of edema. The drug has en associated with peptic ulcer and may re- tivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Mild drug rashes frequently subside with reduction of dosage. However, rash accompanied by fever or other systemic reactions usually requires withholding medication. Purpuric rash has also been reported. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



Dosage in Painful Shoulder: Initial: 3 to 6 capsules daily in 3 or 4 equal doses. Trial period: one week. Maintenance dosage should not exceed 4 capsules daily; response is often achieved with 1 or 2 capsules daily.

Butazolidin® alka Geigy

Capsules

phenylbutazone, 100 mg.; dried aluminum hydroxide gel, 100 mg.; magnesium trisilicate, 150 mg.; homatropine methylbromide, 1.25 mg.

c complete details, lease see full scribing information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

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SAN FRANCISCO, CALIFORNIA · JUNE 16-20, 1968

AMERICAN MEDICAL ASSOCIATION'S 117th ANNUAL CONVENTION · BROOKS HALL

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretion, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, change in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from

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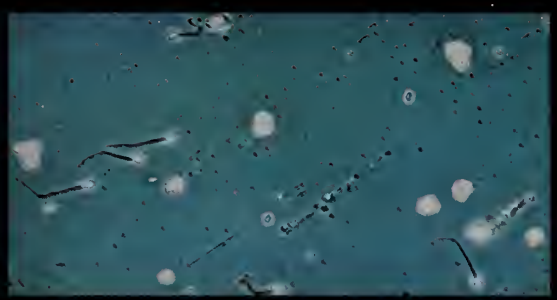
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

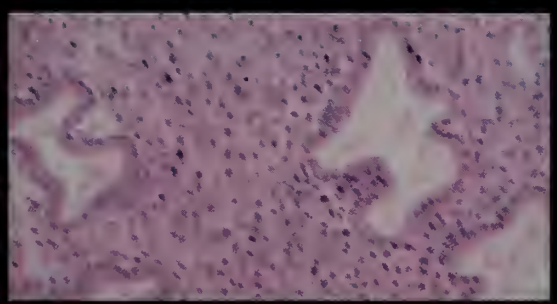
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.



Spermatozoa appear healthy, active, freemoving.

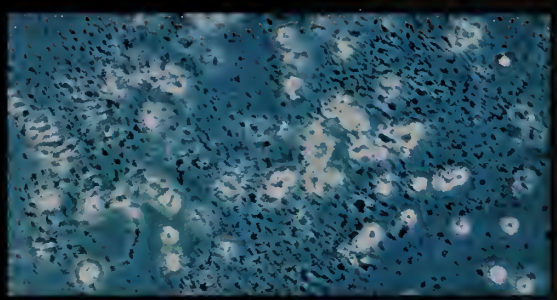


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

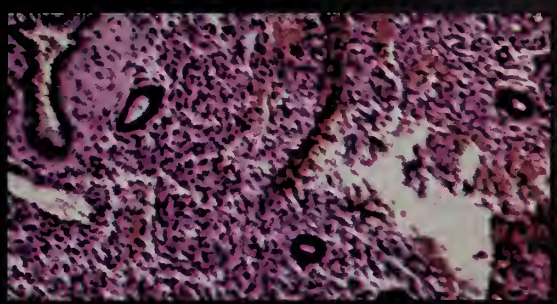
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

Norinyl®-1
(norethindrone 1mg. c mestranol 0.05mg.) tablets

- new low dose of time-proved ingredients
- established norethindrone/mestranol ratio
- lower patient cost

An uncommon steroid for common inflammatory dermatoses

In everyday topical steroid therapy, Synalar produces rapid resolution of inflammation and itching in steroid-responsive dermatoses—and at relatively low cost to the patient.

Advanced molecular design enhances potency

Synalar combines the advantage of earlier corticosteroid compounds with unique structural innovations. As a result, preparations of Synalar 0.01% and Synalar 0.025% have been reported to be more potent topically and significantly more effective than hydrocortisone 1.0%. The unique fluocinolone acetonide molecule provides one of the most useful topical corticosteroids for everyday practice.

Impressive clinical results in a wide range of dermatologic problems

The clinical efficacy of Synalar has been extensively documented in the world literature. Commonly encountered diseases such as allergic and contact dermatitis, eczematous and seborrheic dermatitis, and neurodermatitis respond rapidly to Synalar, often where previous therapy with other topical corticosteroids has failed.

Low patient cost for wider usefulness

With Synalar, a high degree of efficacy does not mean high price. And—a small quantity goes a long way. Thus, your patients can often obtain the "economy" of a hydrocortisone preparation with the proved efficacy of a potent, truly advanced steroid.

Synalar®
fluocinolone acetonide





Turn page for contraindicati[illegible] precautions and side effec

For everyday topical steroid therapy

Synalar® 0.01%

fluocinolone acetonide provides economy in two practical dosage forms

For general use, the most economical and widely applicable concentration of Synalar is 0.01% Cream in a water-washable, vanishing cream base. Synalar Solution 0.01% is especially valuable in dermatoses involving moist, intertriginous areas or hairy sites where creams and ointments do not spread or penetrate readily. Synalar Solution is a unique dosage form—clear, nongreasy, cosmetically elegant.

Product Information

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components. *Precautions:* Synalar preparations are virtually nonsensitizing and nonirritating. However, the solution may produce burning or stinging when applied to denuded or fissured areas. In some patients with dry lesions, the solution may increase dryness, scaling or itching. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have an adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time. *Side Effects:* Side effects are uncommon with topical corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions. In such cases the agent should be discontinued and appropriate measures taken. *Availability:* Synalar (fluocinolone acetonide) Cream 0.025%—5, 15 and 60 Gm. tubes and 425 Gm. jars. Cream 0.01%—15, 45 and 60 Gm. tubes and 120 Gm. jars. Solution 0.01%—20 and 60 cc. plastic squeeze bottles. Ointment 0.025%—15 and 60 Gm. tubes. Neo-Synalar® (neomycin sulfate 0.5% [0.35% neomycin base], fluocinolone acetonide 0.025%) Cream—5, 15 and 60 Gm. tubes.

fluocinolone acetonide—an original steroid from

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Each tablet contains: Codeine Phosphate gr. ½ (Warning – May be habit forming), Phenacetin gr. 2½, Aspirin gr. 3½, Caffeine gr. ½.

■ Despite introduction of synthetic substitutes, efficacy of 'Empirin' Compound with Codeine remains unchallenged.

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Tears without grief

Crying Spells–psychic tension with depressive symptoms?
"I don't know what's the matter with me lately...I cry and I cry... and I really don't know why I do."

A woman often is not conscious of the real reasons for her crying spells or refuses to admit them to herself. On probing, you may find that frequent weeping, like insomnia or neurotic fatigue, often is an expression of psychic tension. She needs sympathy and reassurance, and perhaps a calming agent to help her over her crisis. Consider prescribing Valium (diazepam) for her. It usually reestablishes calmness promptly. Crying spells and other secondary depressive symptoms normally subside as the tension is relieved. Your patient then can cope more easily with stresses to which she is subjected. Valium (diazepam) is generally well tolerated, and on proper mainteenance dosage usually does not impair mental acuity or ability to function. If side effects such as ataxia and drowsiness occur, they usually disappear with dosage adjustment.

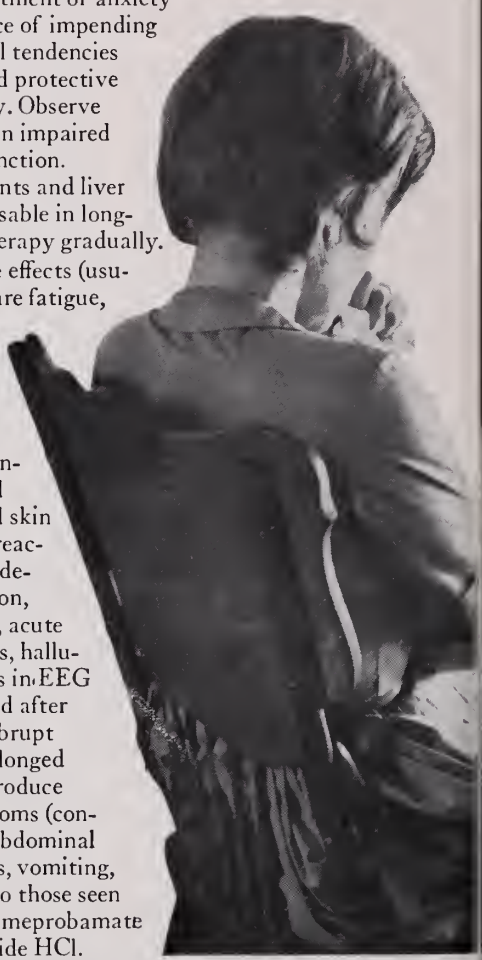


Before prescribing, please consult complete product information, a summary of which follows:

Contraindications: Infants, patients with history of convulsive disorders, glaucoma or known hypersensitivity to drug.

Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.

Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

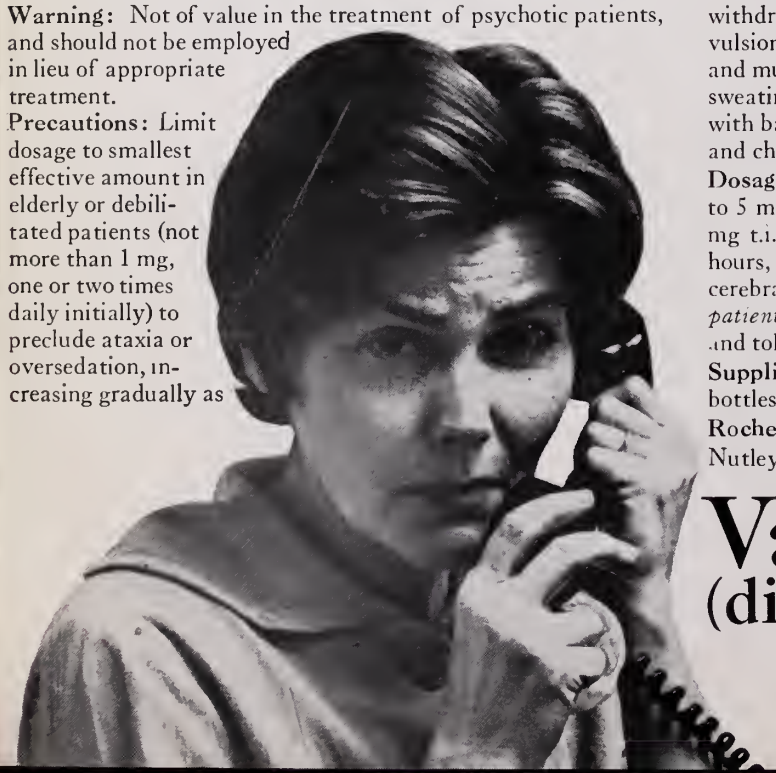


Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

Dosage: *Adults:* Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d. *Geriatric patients:* 1 or 2 mg/day initially, increase gradually as needed and tolerated. (See Precautions.)

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50 and 500.

Roche Laboratories, Division of Hoffmann-La Roche Inc. Nutley, N. J. 07110



ROCHE

Valium® (diazepam) Roche®

useful for the relief of psychic tension with associated depressive symptoms

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BOLETIN

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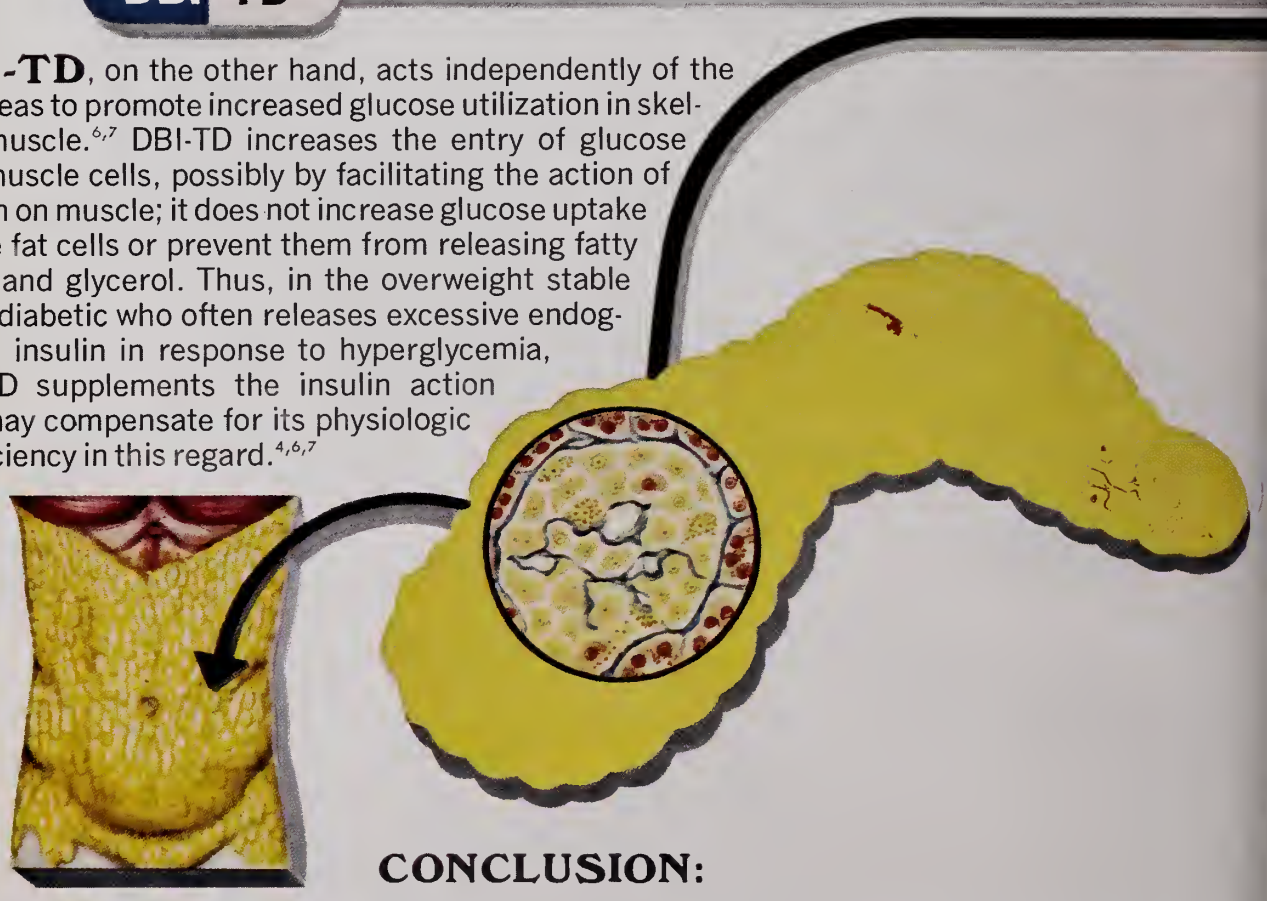
VOL. 60 MARZO 1968 NUM. 3

DBI-TD Does Differ From the Sulfonylureas

SULFONYLUREAS stimulate insulin release by the pancreatic beta cells. Endogenous insulin is often present in excess in stable adult diabetics who are overweight.[1,2] This insulin is apparently inefficient in transporting glucose into skeletal muscle, although it retains its activity in adipose tissue.[3,4] Insulin is not only a potent lipogenic hormone, it is also antilipolytic (suppresses fat mobilization from tissues) and thus can contribute to weight gain.

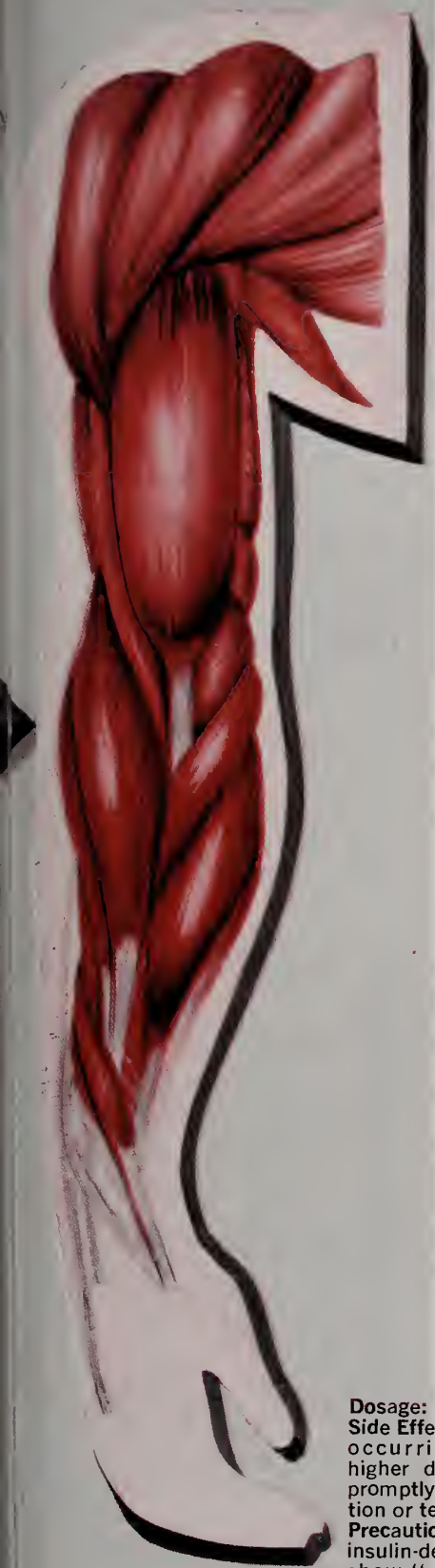
DBI-TD

DBI-TD, on the other hand, acts independently of the pancreas to promote increased glucose utilization in skeletal muscle.[6,7] DBI-TD increases the entry of glucose into muscle cells, possibly by facilitating the action of insulin on muscle; it does not increase glucose uptake by the fat cells or prevent them from releasing fatty acids and glycerol. Thus, in the overweight stable adult diabetic who often releases excessive endogenous insulin in response to hyperglycemia, DBI-TD supplements the insulin action and may compensate for its physiologic inefficiency in this regard.[4,6,7]



CONCLUSION:

DBI-TD acts directly to enhance muscle glucose utilization, whereas sulfonylureas appear to depend upon a supply of insulin releasable from the patient's pancreas for their hypoglycemic effect. Unlike injected insulin or the endogenous insulin released under the stimulus of the sulfonylureas, DBI-T does not promote the conversion of glucose to fat or prevent the mobilization of fatty acids from the adipose tissue depots of the body.



This is Why DBI-TD should be your Drug of First Choice for Most Stable Adult Diabetics

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who are overweight and diet-unresponsive

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ALONE among oral hypoglycemic agents... provides more benefits for most stable adult diabetics

- Lowers blood sugar
- Increases muscle glucose utilization
- Reduces insulin oversecretion
- Promotes gradual weight loss*

*Although anorexia has been suggested as a possible basis for weight loss, controlled studies do not support this. In nondiabetic subjects who are overweight, comparable doses of DBI-TD do not induce weight loss or lower blood sugar.

Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis (acetonuria without hyperglycemia) which must be differentiated from "insulin lack" ketosis which is accompanied by acidosis, and treated accordingly. Lactic acidosis has been reported in nondiabetics and diabetics treated with insulin, with diet, and with DBI. Question has arisen regarding possible contribution of DBI to lactic acidosis in patients with renal impairment and azotemia and also those with severe hypotension secondary to myocardial or bowel infarction. Periodic B.U.N. determination should be made when DBI is administered in the presence of chronic renal disease. DBI should not be used when there is significant azotemia. Any cardiovascular lesion that could result in severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also available:** DBI tablets 25 mg. Consult product brochure.

References: 1. Yalow, R.S. and Berson, S.A.: Diabetes 9:254, 1960. 2. Grodsky, G.M. et al.: Metabolism 12:278, 1963. 3. Gundersen, K. and Antoniades, H.: Proc. Soc. Exp. Biol. Med. 104:411, 1960. 4. Williams, R.H.: Textbook of Endocrinology, Ed. 3, Philadelphia, Saunders, 1962. 5. Gordon, E.S.: Advances Internal Med. 12:66, 1964. 6. Butterfield, W.J.H. and Whichelow, M.J.: Diabetes 11:281, 1962. 7. Searle, G.L. and Cavalieri, R.R.: Presented at 26th Ann. Meet. Amer. Diabetes Ass., Chicago, June 25-26, 1966.

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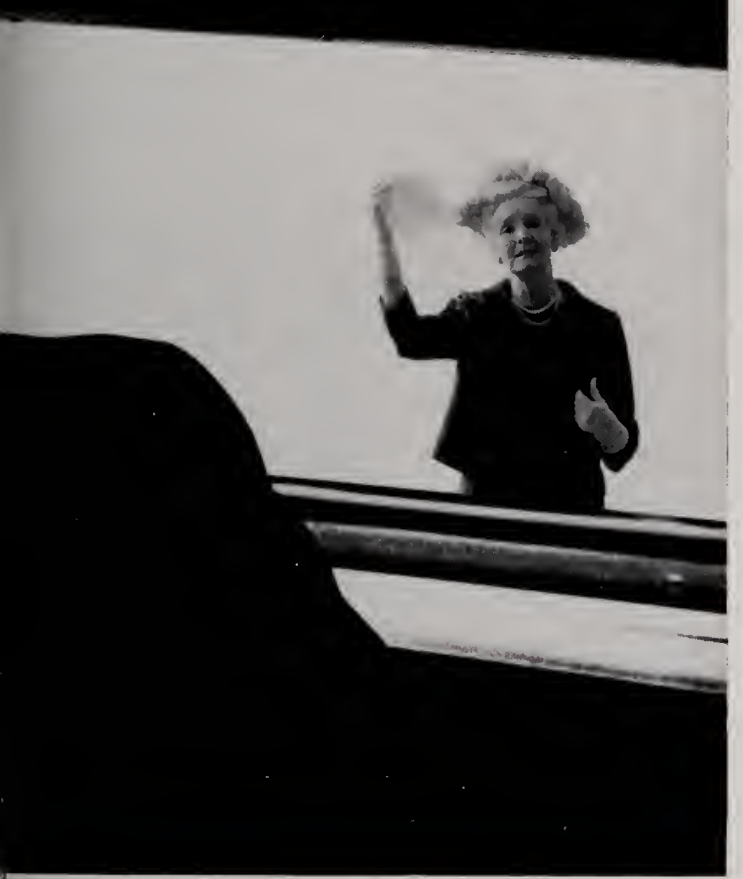
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Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
In rare instances, transient cardia
arrhythmias have occurred in hyp
thyroid patients and in patients re
ceiving thyroid medication when
Tofrānil was added to the regime
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cologic activity of guanethidine a
other related adrenergic neuron-
blocking agents.
The drug is not recommended at
present time in patients under 12
of age.
Adverse Reactions: Dryness of th
mouth, tachycardia, constipation
turbances of accommodation, sw
ing, dizziness, weight gain, urina
frequency or retention, nausea ar
vomiting, peripheral neuritis, mil
parkinson-like syndrome, tremors
rare cases of falling in elderly pa
tients, confusional states (with su
symptoms as hallucinations and
orientation), activation of psycho
schizophrenics and agitation (inc

When a milestone in life is marred by depression...



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Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, in patients with cardiovascular disease, thyroid disorders, increased intraocular pressure, or in those receiving anticholinergics (including antiparkinsonism agents), the special precautions listed in the Prescribing Information should be carefully observed. The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

Tofrānil® imipramine hydrochloride
Geigy

ypomanic and manic episodes)
h may require dosage reduction
or addition of a tranquilizer or
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ptiform seizures, orthostatic
tension and substantial blood
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ura, transient jaundice, bone mar-
depression including agranulocy-
s, sensitization and skin rash
ding photosensitization, eosino-
a, and mild withdrawal symptoms
udden discontinuation after pro-
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pine-like effects may be more
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anticholinergic agents (includ-
ntiparkinsonism drugs).
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g. daily, increased, if necessary,
to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
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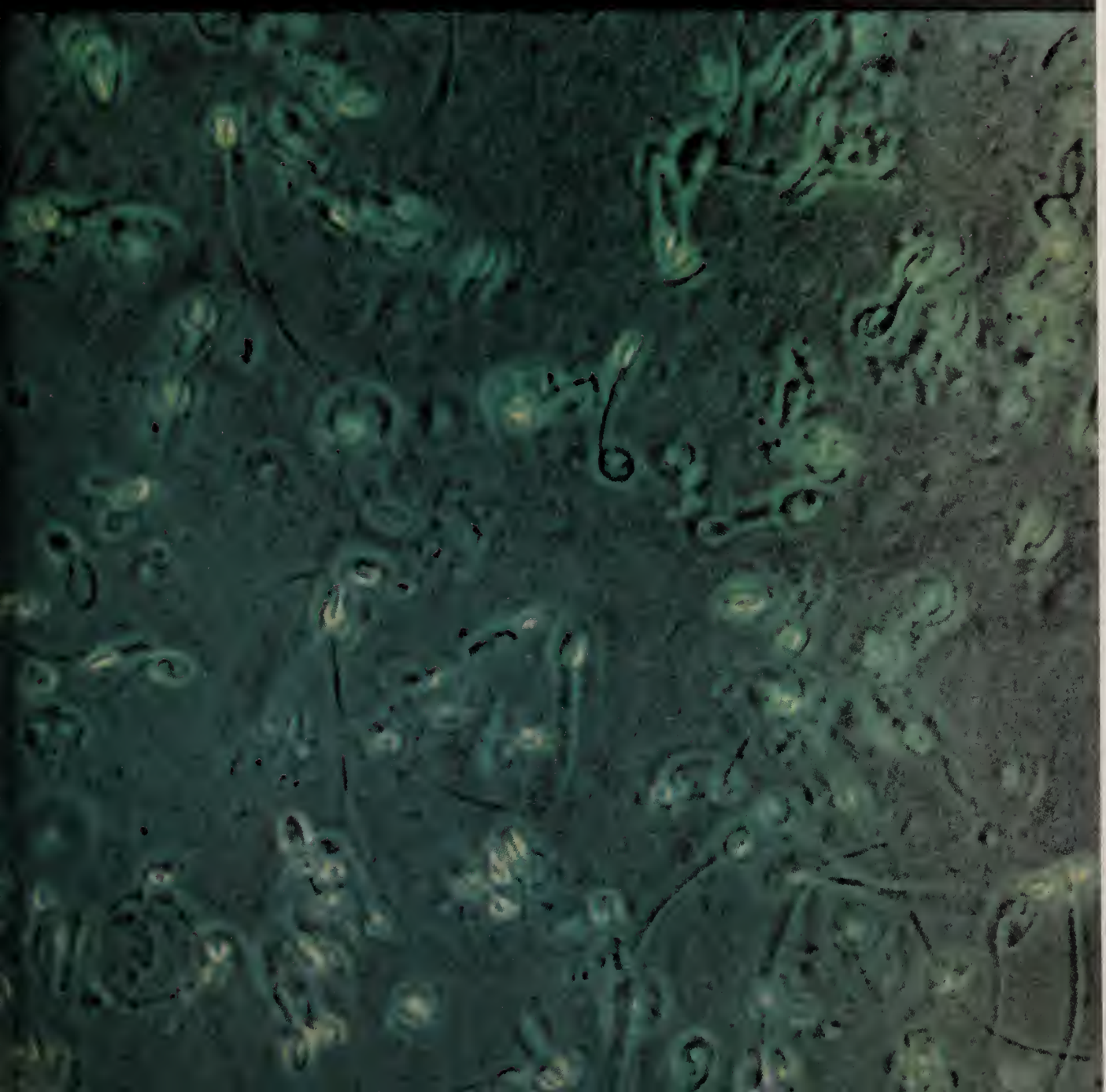
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When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weig (increase or decrease), changes in cervical erosion and cervical secretio suppression of lactation when given immediately postpartum, cholestati jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, change in libido, changes in appetite, cystiti like syndrome, headache, nervousne dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nod sum, hemorrhagic eruption, itching

The following occurrences have bee observed in users of oral contraceptives (a cause and effect relationship has been neither established nor dis proved): thrombophlebitis, pulmona embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine an decrease in T^3 values), metyrapone test, pregnanediol determination.

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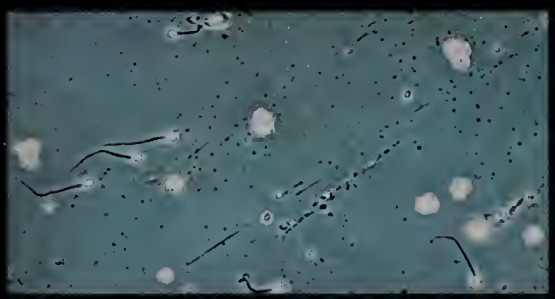
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

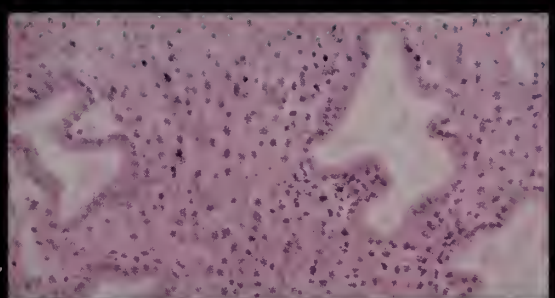
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.



Spermatozoa appear healthy, active, freemoving.

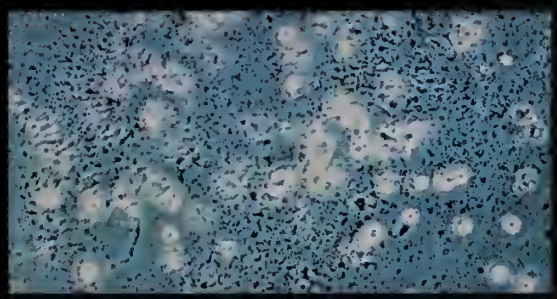


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

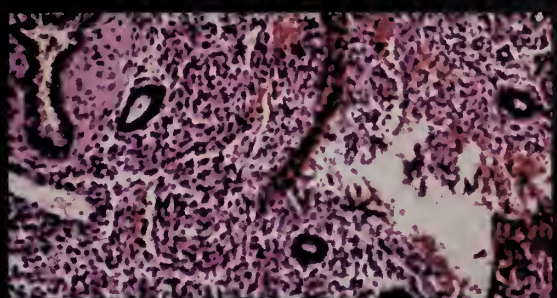
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

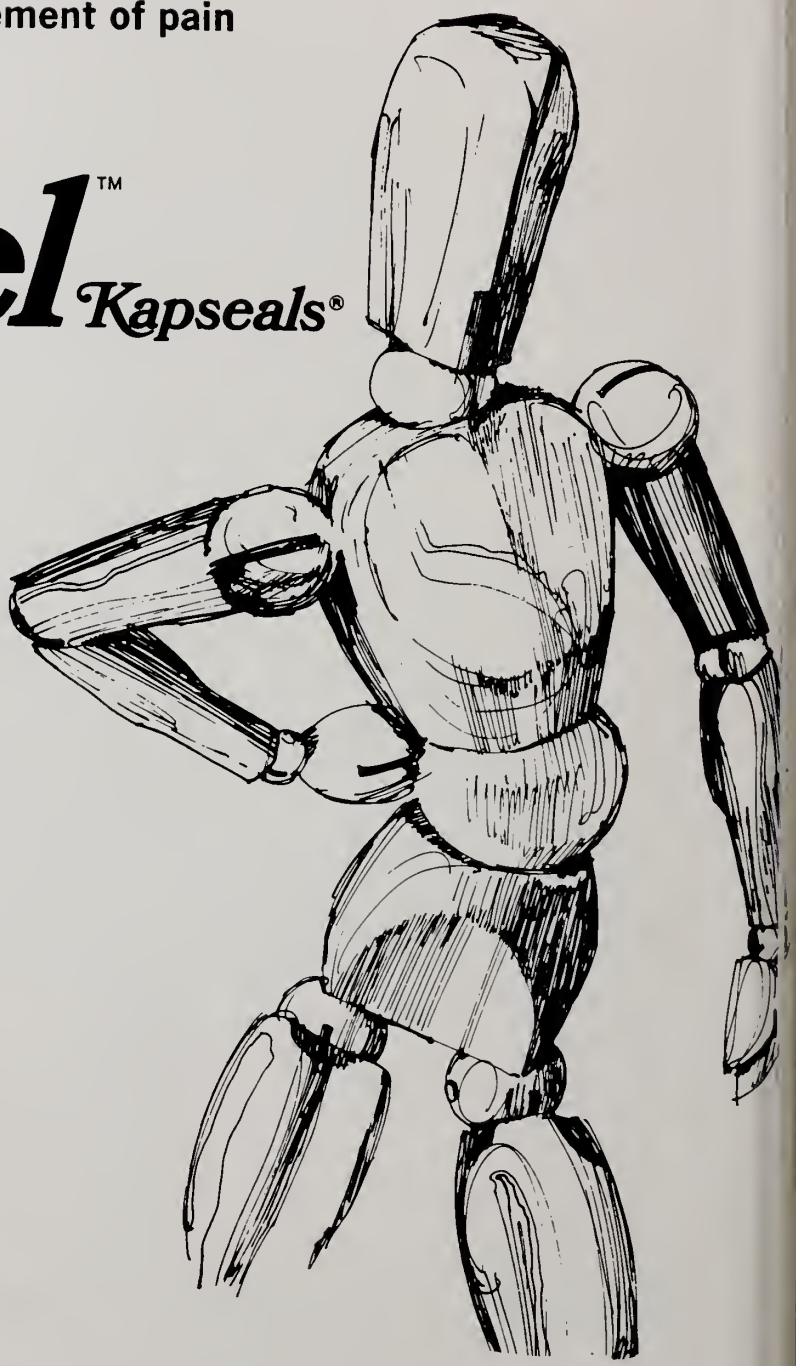
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ROSE BENGAL (^{131}I) EXCRETION TEST IN THE DIAGNOSIS OF OBSTRUCTIVE JAUNDICE IN INFANTS

P. J. Santiago-Borrero, MD
Sergio Irizarry, MD

The clinical picture of obstructive jaundice in the first few months of life can be produced either by biliary atresia or any type of intrahepatic disease. Surgery in the first three months of life is mandatory in cases of atresia of the extrahepatic bile ducts if irreversible damage to liver parenchyma is to be avoided. Neonatal hepatitis and other conditions causing intrahepatic obstructive jaundice are not amenable to surgical treatment. Moreover, in hepatitis the surgical trauma may worsen the course and prognosis of the condition.

In many cases, and sometimes for prolonged periods of time, the patients with neonatal hepatitis have pale stools, colorless duodenal fluid and negative qualitative tests for urobilin and urobilinogen in the urine and stool. Other conventional liver-function tests are often of little use in the differentiation between intrahepatic and extrahepatic biliary obstruction. (1, 2) This is so because many of the infants with obstructive jaundice secondary to hepatitis seem to have nearly as complete and prolonged biliary obstruction as those with extrahepatic biliary atresia. Needle biopsy of the liver is not without risk and gives inconclusive results many times (3). At present, surgical exploration and direct cholangiography and histologic examination of an open biopsy specimen are the most accurate means of differentiation.

From the Department of Pediatrics, School of Medicine, and the Puerto Rico Nuclear Center, University of Puerto Rico.

The degree of biliary obstruction can be assessed by rose bengal clearence tests used to measure the liver uptake and the excretion of the dye via the stool after its intravenous administration (4). The injected dye is excreted exclusively through the biliary system and reabsorption from the gastrointestinal tract does not occur. (5) Reliable measurement of the dye is possible, and is facilitated further by labeling the rose bengal with ^{131}I. In normal subjects the peak concentration in the liver is reached in ten to thirty minutes, and the dye can be detected in the gastrointestinal tract within twelve to fifteen minutes of the injection. The peak concentration in the bile is reached in thirty minutes (5).

In patients with parenchymal liver damage the rate of uptake of the dye by the liver is reduced. In partial biliary obstruction the arrival time of the dye in the intestine is longer. In cases of complete biliary obstruction the dye does not reach the intestinal tract. (4, 5)

Taplin *et al* (4) first used ^{131}I — labeled rose bengal measuring by external counting the rate of uptake by the liver. Nordyke (5) modified this technique further by counting over the intestine and the head, as well as over the liver, in order to meas-

ure the pattern of excretion into the gut. Brent and Geppert (6, 7) introduced a further modification of the test by measuring the excretion of the ^{131}I — labeled rose bengal in the stool and urine. This latter technic is eminently suited for the assessment of the degree of biliary obstruction. However, this procedure is not easily carried out in infants due to the difficulty in collecting urine quantitatively and feces free of urine in this age group. The technic described by Nordyke (5) is perhaps less sensitive than the quantitative method of Brent and Geppert (6, 7) but it is more practical and easy to be adapted to the laboratory facilities of a general hospital.

This report presents the experience obtained in the determination of intestinal excretion of ^{131}I — labeled rose bengal, as measured by external scintillation counting, in 10 cases of neonatal obstructive jaundice in the University Hospital in Río Piedras, Puerto Rico in 1966 and 1967.

Materials and Methods

Ten infants 4 months of age admitted with obstructive jaundice to the University Hospital from July 1966 to December 1967 were included in this study.

The diagnosis of neonatal hepatitis was made clinically in infants who presented the picture of jaundice of variable degree, with a significant fraction of the bilirubin of the "direct" type, appearing a few weeks or months after birth and clearing up slowly subsequently.

Besides routine liver function studies, the patients had ^{131}I-labeled rose bengal excretion tests performed during the hospitalization. Three patients had a second rose bengal excretion test performed one to four weeks after the original one.

Under sedation with chloral hydrate, the patients were fixed in the supine position and they were given ^{131}I-labeled rose bengal (^{131}I-RB) in a dose of 15 μc per square meter (average dose, 4 μc) intravenously through an intravenous infusion set. A scintillation probe with a one-inch sodium iodide crystal and a cylindrical one-inch diameter collimator was placed directed at the liver on the right mid axillary line, aligned with the left axilla. A second similar counter was placed just to the left and above the umbilicus making sure that the liver border was out of the field of vision of the probe. Both counters were connected to a rate meter and to two synchronized constant registering devices set at a proper speed and scale. At the time of intravenous injection of the ^{131}I-RB, the registering device was turned on and the radioactivity in the liver mass and in the intestine was detected and recorded continuously for a period of two and a half hours. Lugol's solution was given per mouth one day prior to and several days after the test to block the thyroid gland.

The ^{131}I-labeled rose bengal* is supplied commercially as a sterile solution having a relatively high specific activity. These concentrated preparations are then diluted with sterile isotonic saline solution to make up individual doses containing the desired volume and radioactivity.

Because of the small radioiodine dose required for this technique with the highly sensitive detecting equipment and the rapid clearance of this labeled dye from the liver, the radiation dose delivered to the normal infant is within the lower millirad range (8). Even with complete biliary tract obstruction, the maximum dose will remain below the range of diagnostic X-rays (9).

Results

Table I presents data on the ten patients with obstructive jaundice studied by the ^{131}I —rose bengal excretion test. Eight of them were male babies. The age varied from 3 weeks to 3½ months, and the body weights from 3½ to 11 pounds. The duration of jaundice prior to admission ranged from 1 week to 3 months. The total bilirubin varied from 5.3 to 22 mg. %, the direct fraction accounting for over 50% of the to-

*^{131}I *Rose bengal was obtained from Abbot Laboratories, Oak Ridge, Tennessee.*

tal in all cases except in patient number 6 in whom it was 46%. The serum glutamic pyruvic transaminase (SGPT) varied from 24 to 580, and the glutamic oxalacetic (SGOT) from 30 to 720 units at the time of, or a within few days of the ^{131}I –RB excretion test.

60 minutes and there is no significant discharge, indicating some liver damage and defect in the excretory function. The curve of abdominal radioactivity shows a small early drop due to liver clearance of the dye from the blood. But thereafter, the curve remains flat demonstrating failure of en-

TABLE I: DATA ON TEN INFANTS WITH OBSTRUCTIVE JAUNDICE

Case No.	Age	Weight (lbs.)	Duration of Jaundice	Total Bilirubin mg %	Direct Bilirubin mg %	Alkaline Phosphatase K. A. units	SGPT units	SGOT units	^{131}I-RB Excretion Test	Final Diagnosis
1	3 mos.	11	2½ mos.	4.6	3.8	10.7	90	72	Neg. #	Biliary Atresia*
2	2 mos.	10	2 weeks	7.9	4.8	23.4	58	72	Pos.	Hepatitis
3	1½ mos.	11	3 weeks	5.6	4.5	6.3	24	30	Pos.	Hepatitis
4	3 mos.	8½	1½ mos.	5.8	3.5	—	27	43	Pos.	Hepatitis
5	20 days	3½	1 week	19.3	11.1	—	106	232	Neg.	Hepatitis /
6	2 mos.	7½	2 weeks	5.3	2.4	44.5	580	720	Pos.	Hepatitis
7	3½ mos.	11	3 mos.	11.2	6.6	52.5	185	106	Neg.	Biliary Atresia*
8	1 mo.	5½	1 week	22.0	14.5	7.8	80	100	Neg.	Hepatitis /
9	3 weeks	6½	1 week	11.6	6.0	24.7	230	330	Pos.	Hepatitis
10	2 mos.	6	1 week	12.0	7.2	13.8	225	159	Neg.** Pos	Hepatitis

Negative ^{131}I-RB excretion test means failure of intestinal entrance.
** Cases of biliary atresia were diagnosed by laparatomy and open liver biopsy.*
/ Patients died after jaundice cleared up. Autopsy in one confirmed hepatitis.
*** First ^{131}I-RB test was negative, but repeat test was positive. Jaundice cleared up later.*

The curve of liver activity obtained on an infant with no recognizable liver or biliary disease shows a fast and progressive rise right after the intravenous injection of ^{131}I – rose bengal, due to the uptake of the dye by the liver, followed by a slow loss of radioactivity due to the discharge of the tracer into the biliary system and intestine. The curve obtained over the umbilical area represents first the activity present in the large blood vessels of the abdomen shortly after injection of the dye. This blood radioactivity decreases for the first ten minutes due to the clearance of the tracer by the liver. After that period of time, the curve of abdominal radioactivity in normal persons shows a rise due to the entrance of ^{131}I –rose bengal into the intestine (Fig. 1). In two patients with proven biliary atresia the liver radioactivity rises slowly reaching a plateau in about

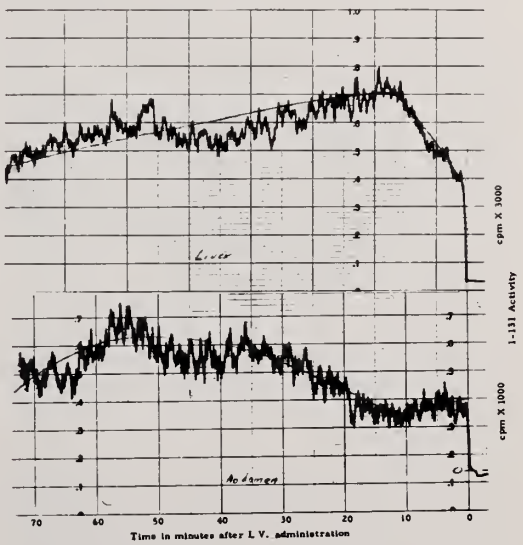


Fig. 1: Normal ^{131} I rose bengal hepatobiliary function study.

trance of the dye into the intestine (Fig. 2). A premature baby with hepatitis, prov-

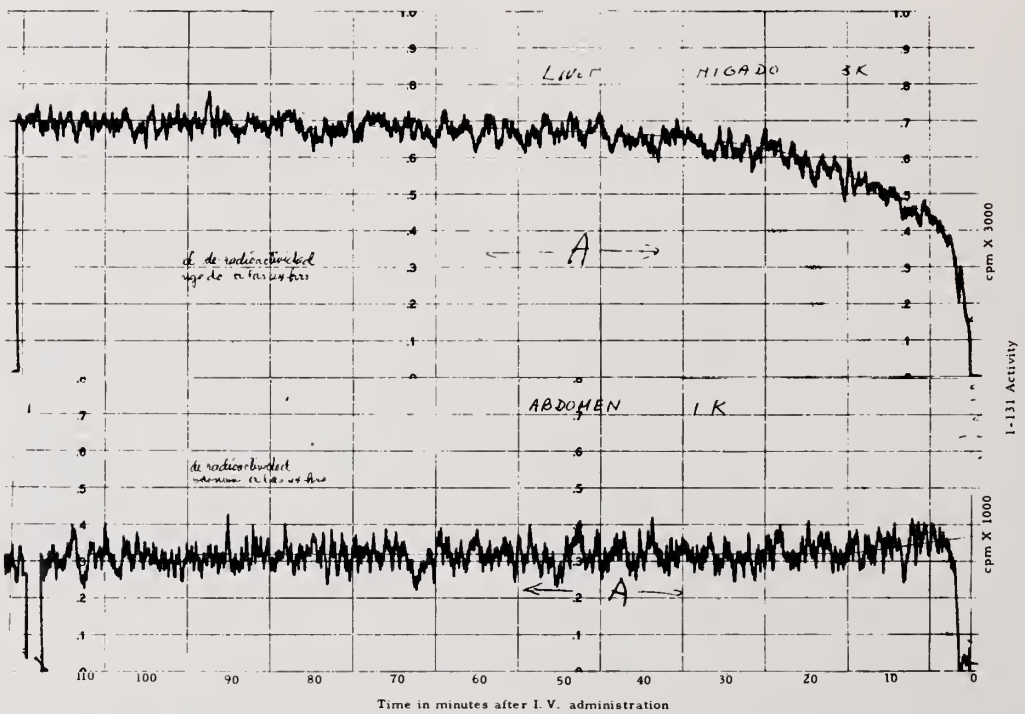


Fig. 2: Typical ^{131} I rose bengal hepatobiliary function study in a patient with congenital biliary atresia.

en on postmortem examination, barely showed intestinal entrance of the ^{131}I –rose bengal at 30 minutes (Fig. 3). However, a study repeated two weeks later on the same patient showed definite entrance of the dye into the intestine (Fig. 4).

Infants with obstructive jaundice due to neonatal hepatitis usually showed markedly delayed but definite liver discharge and intestinal entrance of the ^{131}I –RB tracer (Fig. 5).

One patient who had a clinical picture perhaps more suggestive of hepatitis than of biliary atresia, was lost to follow up (case 4). The ^{131}I –RB excretion test showed incomplete biliary tract obstruction and therefore it was compatible with hepatitis. Five patients whose clinical pictures was compatible with either biliary atresia or hepatitis had no evidence of intestinal entrance of the ^{131}I –RB. In one of them, a second study two weeks later showed entrance of the dye into the gut, and subsequent observation and follow up showed clearance of the jaundice. Two other patients with negative ^{131}I –RB excretion tests were premature babies in whom the jaundice cleared but they finally died. Autopsy in one of them showed evidence of hepatitis. Although autopsy was not obtained in the second one, the course prior to death ruled out biliary atresia. The other two patients who had negative

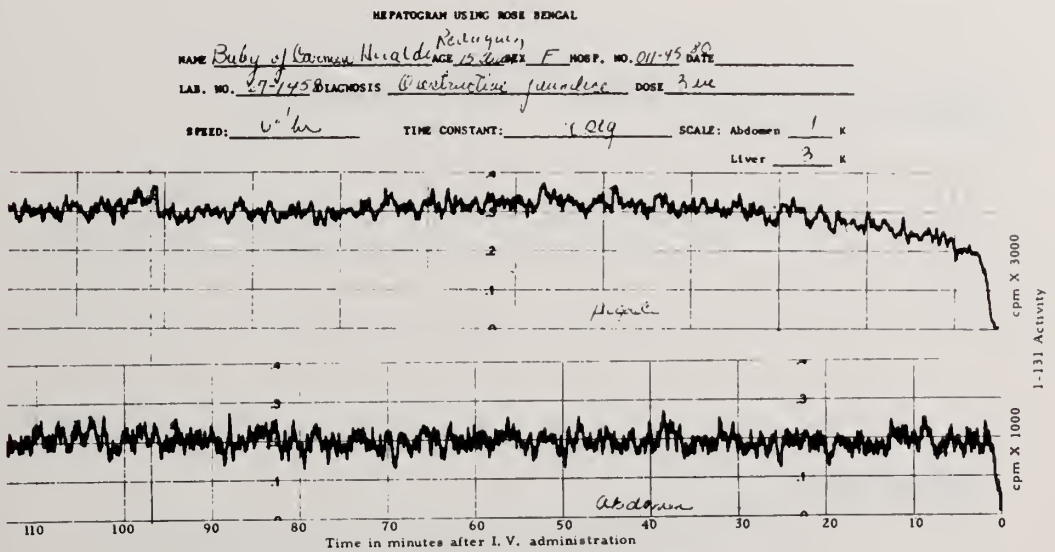


Fig. 3: ^{131} I rose bengal hepatobiliary function study in a patient with neonatal hepatitis which sho wed minimal entrance of the tracer into the intestine at thirty minutes.

^{131}I –RB excretion tests had biliary atresia confirmed at exploratory laparotomy.

Discussion

It is generally accepted that one cannot differentiate congenital biliary atresia from obstructive jaundice with patent extrahepatic ducts in infants by the conventional clinical and laboratory criteria. It seems that in many cases of neonatal hepatitis there occurs complete or nearly complete intrahepatic biliary obstruction for variable periods of time, or though perhaps the obstruction is not quite as complete as in biliary atresia, the routinely used qualitative tests and observation are not sensitive enough to make the differentiation.

Studies reported by Brent and Geppert (6) and Ghadimi and Sass-Kortsak (8) show that quantitative measurement of fecal (72 hour) excretion of ^{131}I –labeled rose bengal is the most useful criteria for the diagnosis of obstructive jaundice in infancy. Fecal excretion of 10% or more of the dose given intravenously should be regarded as evidence of incomplete biliary obstruction, which is incompatible with the diagnosis of biliary atresia. If the fecal dye excretion is five per cent or less of the dose given the patient is most likely suffering from atresia of the extrahepatic bile ducts and should have the benefit of early surgical exploration for possible correction of the defect (8). Although with such a policy one may occasionally operate on a patient with complete biliary shutdown and yet with patent extrahepatic ducts, the value of the test is that by its use one can avoid unnecessary surgical intervention in probably most of the patients with intrahepatic disease (8).

However, techniques for obtaining quantitative stool collection for seventy-two hours uncontaminated by urine are cum-

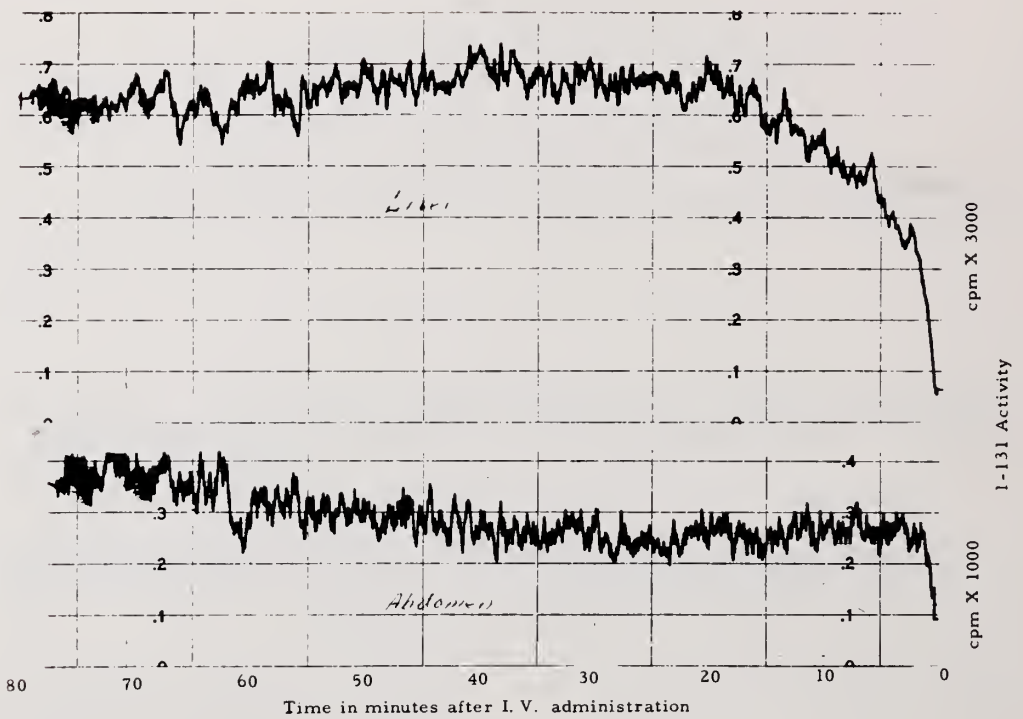


Fig. 4: 131 I rose bengal hepatobiliary function study in a patient with neonatal hepatitis two weeks after obtaining the tracing presented in figure 3.

bersome and not routinely feasible in general hospitals. This, plus the risk of contamination and transmission of infectious hepatitis to personnel handling stool specimens, limits the use of the quantitative ^{131}I —rose bengal excretion test.

White *et al* in 1963 (9) studied the hepatobiliary function in fifty children by measuring radioactivity over the heart, intestine and liver after the intravenous administration of ^{131}I —rose bengal. The series included fifteen children with complete or nearly complete extrahepatic biliary obstruction proved by laparotomy, and fourteen patients with hepatitis diagnosed clinically. Out of twelve children who exhibited no intestinal entrance of ^{131}I —RB, eleven had proved biliary atresia and one had inspissated bile syndrome. Three patients with hypoplastic biliary systems, choledocal cyst, and partial obstruction of the hepatic bile duct by an aberrant vessel had delayed arrival time, and less than normal activity in the intestine in sixty minutes. The authors found only a variable decrease in the quantity of activity reaching the small bowel, and normal appearance time of rose bengal in the intestine in all the fourteen patients with hepatitis. However, this series included only four infants with neonatal hepatitis, who are the ones most likely to present a picture of obstructive

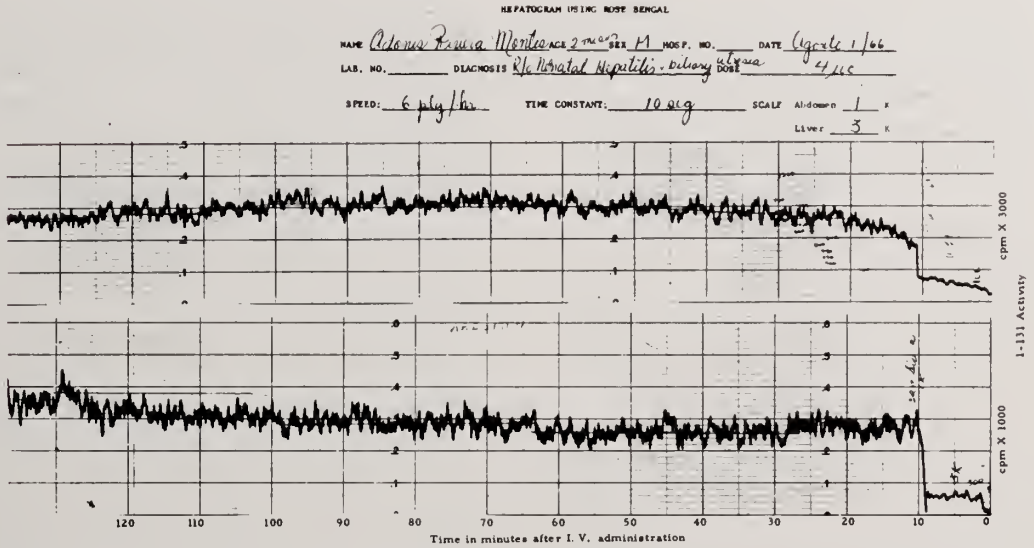


Fig. 5: Typical ^{131} I rose bengal hepatobiliary function study in a patient with neonatal hepatitis.

jaundice indistinguishable from biliary atresia. It is conceivable that in a larger group of infants with neonatal hepatitis some of them might have failed to show passage of ^{131}I –RB into the intestine some time during the course of the illness.

The results presented in this small series, which includes twice as many cases of neonatal hepatitis as White's, do not agree entirely with his experience (9). Four patients out of ten examined showed a negative ^{131}I –RB excretion test. However, two of them subsequently recovered from the jaundice, and thus the clinical course ruled out the diagnosis of biliary atresia.

The ^{131}I –rose bengal excretion test performed by external counting over the liver and intestine did not always differentiate obstructive jaundice due to intrahepatic disease from that due to biliary atresia in infants. However, on the first examination the test screened out more than half of the cases of hepatitis, and on repeat examination another patient was identified. So, the test was effective in identifying three fourths of the patients with obstructive jaundice due to intrahepatic disease, and thus it helped greatly to reduce the observation period in the hospital and to discard the possibility of surgical intervention in these patients. The risk of operating on some patients with neonatal hepatitis is reduced by this test but it is still present. Close observation of the patient and repeat rose bengal excretion tests will lessen that problem.

This modified test does not require any specialized facilities beyond those of a basic radioisotope laboratory. It is simple to perform and it may be repeated several times during the observation period without undue risk to the patient.

Summary

The liver function and patency of the biliary ducts can be assessed by counting

the radioactivity over the liver and intestine after administering rose bengal tagged with radioactive iodine ^{131}I intravenously.

Ten infants with obstructive jaundice in the first four months of life were studied by the ^{131}I —rose bengal excretion test. Six of them showed passage of the tracer into the intestine, and subsequent follow up proved them to have hepatitis. Four out of ten patients failed to show intestinal entrance of the labeled rose bengal. However, only two of them were proved to have biliary atresia.

The ^{131}I —labeled rose bengal excretion test as measured by external counting over the liver and intestine helped to separate three fourths of the patients of neonatal hepatitis from those with congenital biliary atresia. But two patients with neonatal hepatitis showed a negative rose bengal excretion test.

The ^{131}I —rose bengal excretion test, as described in this report, helps to separate most of the patients with neonatal hepatitis from those with biliary atresia, and thus it helps to shorten their hospitalization and to avoid unecessary surgical exploration in most patients with obstructive jaundice in the neonatal period.

Resumen

La función hepática y el drenaje a través de los conductos biliares se pueden evaluar midiendo la radioactividad sobre el hígado e intestino después de administrar endovenosamente rosa de bengala marcada con yodo radioactivo (^{131}I).

Diez pacientes con ictericia obstructiva en los primeros cuatro meses de vida fueron estudiados por la prueba de excreción de rosa de bengala-^{131}I. Seis de ellos demostraron entrada del trazador al intestino y en seguimiento posterior evolucionaron como casos de hepatitis. Cuatro de los diez pacientes no demostraron entrada de la rosa de bengala marcada al intestino. Sin embrago, sólo dos de ellos probaron ser casos de atresia biliar.

La excreción de rosa de bengala-^{131}I comprobada por medición externa sobre el hígado y el intestino, ayudó a separar tres cuartas partes de los casos de hepatitis neonatal de los pacientes con atresia biliar congénita. Pero dos pacientes con hepatitis neonatal presentaron una prueba de excreción de rosa de bengala-^{131}I negativa.

La prueba de excreción de rosa de bengala-^{131}I según se describe en este informe ayuda a separar la mayor parte de los pacientes con hepatitis neonatal de aquellos infantes con atresia biliar extrahepática, y así ayuda a acortar la hospitalización y evita la exploración quirúrgica innecesaria en muchos pacientes con ictericia obstructiva en el período neonatal.

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BEPHENIUM HYDROXYNAPHTHOATE IN THE TREATMENT OF HOOKWORM DISEASE IN INFANCY

Margarita C. Costas, MD
C. A. Torres de Vega, MD

Hookworm disease during early infancy carries a grave prognosis. The cause of death appears to be massive gastrointestinal hemorrhage (1, 2). Even when the diagnosis has been established early, specific therapy with tetrachlorethylene and concomitant supportive therapy has been of no benefit (1, 2).

During the past two years we have encountered three infants with severe anemia and gastrointestinal bleeding associated with severe hookworm infection who responded dramatically to transfusion of packed red cell and therapy with bephenium hydroxynaphthoate. The success of this treatment has prompted the present report.

Bephenium hydroxynaphthoate is a quaternary ammonium compound which is poorly absorbed from the gastrointestinal tract. The main side effects are dizziness, nausea, vomiting, abdominal discomfort, diarrhea and headache (12). The usual dose is 5 grams of the dispersible granules for children over 2 years and 2.5 grams for those under 2 years given as a single dose and repeated in one week if necessary. This dosage schedule has been associated with minimal side effects.

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Case Summaries

Case 1:

A 44-day-old male infant was admitted for the first time to the University Hospital on August 29, 1964 with the chief complaint of increasing pallor of three weeks' duration.

The baby is the youngest of a family of six children, four of which are suffering from severe anemia and parasitosis. The mother has rheumatic heart disease and was found to be anemic during the last pregnancy. The patient weighed 7 lb. 7 oz. at birth and was asymptomatic during the first three weeks of life.

The family lives in a wooden house in Carolina, Puerto Rico, without electricity, water or sanitary facilities. The father is unemployed, and they are on relief.

The physical examination on admission revealed a well developed but very pale infant weighing 8 lb. 6 oz. The chest was clear and the heart revealed a grade II systolic murmur best heart at the apex. The liver was palpated 3 cm below the right costal margin. There was a left clubfoot.

The blood count on admission revealed a hemoglobin of 5.4 g with a white blood count of 20,000/cu. mm. with 7% eosinophiles. On October 3 the WBC was 28,000 with 26% eosinophiles. The stools were bloody and on microscopic examination showed hookworm eggs. The bone marrow studies revealed a normoblastic hyperplasia of the red blood cell series with changes compatible with severe iron deficiency; the granulocytic series showed giant bands, market eosinophilia and normal megakoryocytes and platelets.

On admission the patient was given small packed red blood cell transfusions, and the hookworm disease was treated with tetrachlorethylene 0.4 ml. orally. Bloody stools persisted, and on

September 3, he passed large amounts of fresh blood per rectum and went into shock. On September 18, repeated stool examination reveled a Beaver's egg count of 60,000 hookworm eggs per gram of stool. (3) Another course of tetrachlorethylene therapy (0.4 ml.) was then administered, but in spite of this therapy and of adequate supportive treatment, the stools continued to be grossly bloody and positive for severe hookworm infection. On October 20, bephenium granules, 2.5 grams, was given by gastric tube. The hookworm egg count prior to therapy was 45,000 eggs per gram of stool, and three days post-therapy, the stools were negative for ova and parasites. During the first day post- therapy the child passed many adult worms identified as *Ancylostoma duodenale.* Following bephenium therapy the stools became normal and on October 27 the infant was discharged completely asymptomatic with a hemoglobin of 11.0 grams.

Case 2:

A 14 month old boy from Carolina, Puerto Rico was admited to the University Hospital on December 1, 1966. He had a one-month history of increasing pallor, vomiting and bloody diarrhea preceded by an episode of respiratory distress.

The infant is the youngest of a family of nine children. He was born after a nine months normal pregnancy. He was noticed to be pale and to have a yellowish tinge of the conjunctine since birth. At the age of three months he was hospitalized at the Carolina Health Center because of anemia.

The physical examination on admission revealed severely pale and malnourished infant weighing 10 pounds who was in shock. He was passing grossly bloody stools. The respiratory rate was 36 per minute. The lungs were clear. The heart rate was 132, and there were no murmurs. The liver was palpable 3 cm below the right costal margin.

Admission studies revealed a hemoglobin of 1.6 g/100 ml, a WBC of 10,000,/cu mm, and a differential count of 54% neutrophils and 46% lymphocytes. On December 8, a mild peripheral eosinophilia of 10% was detected. The admission bone marrow examination showed changes of severe iron deficiency anemia, normal megakaryocytes and platelets, and a marked osinophilia. The eosinophils showed ordely maturation. The stools showed severe hookworm and trichuris infection, with Beaver's stool egg counts of 32,000 and 50,000 eggs per gram of stools, respectively.

On admission 50 cc of packed red blood cells was given, after which the patient's state of shock improved. Following general supportive therapy which included several small blood transfusions, bephenium granules, 2.5 grams, was given orally on December 6. He tolerated the medication well and on December 12 the stools were non-bloody and negative for hookworm eggs, though still showing a Beaver's stool egg count of 37,500 trichuris eggs per gram of stool. Stool collection following bephenium therapy revealed adult worms identified as *Ancylostoma duodenale.* Hexylresorcinol % retention enemas were given as treatment for the trichuriasis. Upon discharge on December 25, the infant was asymptomatic and gaining weight, and the stools were negative for ova and parasites.

Case 3:

This 6 month old male infant was admitted to the University Hospital on December 5, 1966, with a history of dark colored liquid stools since birth and rapidly increasing pallor of one month's duration. During the month prior to admission he had received iron preparations both orally and parenterally without improvement.

The infant is the youngest of a family of six children living in Carolina, Puerto Rico in a one-room wooden house with electricity and latrine but without running water. Three siblings ages 4.5 and 6 years suffer from anemia and parasitosis.

Physical examination on admission revealed a well developed pale infant passing black liquid stools containing bright red blood. The chest was clear. The liver was palpated 3 cm below the right costal margin and 2.5 cm below the xyphoid; the spleen was not palpable. Rectal examination was negative except for the stools described above.

Admission blood count showed a hemoglobin of 3.9g/100 ml and a white blood cell count of 46,200/cu mm, 64% of which were eosinophiles. The bone marrow revealed megakaryocytes with adequate platelet production, erythrocytic hyperplasia with normoblastic development, and marked eosinophilia. The iron stain revealed no stored iron. Admission Beaver's stool egg count was 50,000 hookworm eggs per gram of stool.

On admission the patient received transfusions of packed red blood cells. On December 6, be-

phenium granules, 2.5 grams, was given orally. Following the first dose of the drug the patient passed many adult hookworms which were identified as *Ancylostoma duodenale*. On December 12, the stool egg count was 3,000 hookworm eggs per gram of stool. On December 17 and 27 bephenium therapy (2.5 grams) was repeated. From December 27 and until discharge on January 9, 1967 he had a productive cough accompanied by bilateral coarse rhonchi. On discharge he was asymptomatic with 9.5 gm of hemoglobin and the stools were well formed, non bloody, and negative for ova and parasites.

Discussion

In the three patients presented here the gastrointestinal bleeding promptly subsided following successful antihelminthic therapy. Zimmerman (4) in his article on autopsy findings in 21 children from Guam with fatal hookworm disease described severe inflammatory lesions involving mainly the jejunum and the upper ileum. The mucosa of the jejunum frequently disclosed many adult hookworm attached to the villi and areas of deep ulcerations adjacent to the worms.

Patient No. 1 presented here and other reported cases of ages below 3 months (5) bring up the question of the manner of acquiring the infection at such an early age. Certainly acquisition of the infection by the usual method of skin contact with contaminated soil seems unlikely. One possible explanation is given by Stoll (6) who established the fact that bed clothes, when contaminated with infective fecal matter and allowed to remain damp and unwashed for some days, will harbor appreciable numbers of filariform hookworm larvae. In this way patients can come in contact with .the larvae even at the moment of birth. Since the larva requires approximately 45 days to mature into an adult, the presence of hookworm eggs in infants below the age of one month as reported in the literature (5) strongly suggests the possibility of a transplacental route of infection. In dogs transplacental infection with *Ancylostoma caninum* has been well substantiated (7,8).

Peripheral blood eosinophilia of 10% or more was present in the 3 patients of our series and was also encountered in the two infants reported by Alvarez and Torres (2). It is interesting that the patients most severely ill on admission (patients 1 and 2) showed the most insignificant peripheral eosinophilia in contrast to the striking eosinophilia encountered simultaneously in the bone marrow. A similar situation has been observed in children with the visceral larva migrans syndrome when under severe stress or when given steroid therapy (9). In severe infection the larval migratory phase of hookworm disease (10) may manifest as a clinical picture indistinguishable from the visceral larva migrans syndrome associated with other parasites.

It is highly significant that *Ancylostoma duodenale* was the only hookworm species encountered in the three infants, since *Necator americanus* has been identified as the species most common in Puerto Rico. Since the three patients came from the same coastal town, Carolina, it is likely that *Ancylostoma duodenale* may occur in a pure form in certain coastal areas of the island. An alternative is the possibility of a changing pattern in the island with a tendency for *Ancylostoma duodenale* to predominate over *Necator americanus*. This could be due to the wide use of tetrachlorethylene in the treatment of hookworm disease, since this drug appears to be less ef-

fective against *Ancylostoma* than against *Necator.*

Severe gastrointestinal bleeding as a manifestation of hookworm disease appears to be related not only to the age of the patient but also to the hookworm species involved. A similar clinical picture was reported in a 40 years old Puerto Rican patient who had severe *Ańcylostoma duodenale* infection. (11) In Zimmerman's series (4) the species of parasite besides the age of the patient was considered a prime factor in the production of fatal hookworm disease. In his series 93% of the hookworms were *Ancylostoma duodenale.*

The excellent response to bephenium therapy shown by the three infants is most probably related to the species of hookworm involved. In one patient bephenium therapy was definitely life saving, since he had failed to respond to repeated tetrechlorethylene therapy and almost died from severe gastrointestinal hemorrhage, for which he had required eleven blood transfusions. Other studies have borne out the fact that bephenium is more effective than tetrachlorethylene against hookworm infections due to *Ancylostoma duodenale.* (12)

In view of these findings we recommend bephenium as the drug of choice for the treatment of hookworm disease during infancy and possible at other ages if gastrointestinal bleeding is the presenting clinical picture. We also recommend its use in patients with hookworm disease who have not responded well to tetrachlorethylene. In all of these patients the presence of *Ancylostoma duodenale* rather than of *Necator americanus,* should be strongly suspected.

Acknowledgments:

*Bephenium was supplied by Burroughs Wellcome and Co., U.S.A. as Alcopara.

Dr. J. Oliver González, of the Parasitology Laboratory of the U. P. R. School of Medicine, and Dr. Antonio Barquet Chediak, of the Medical Center Laboratory, identified the adult hookworms.

Summary

The case histories of three children with massive infection with *Ancylostoma duodenale* are presented. Two of them were less than one year of age; the other 14 months old. They presented a similar clinical picture with severe anemia, bloody stools and eosinophilia. They were treated with bephenium hydroxynaphthoate, with marked clinical improvement and disappearance of parasitosis. Previous tetrachlorethylene therapy had resulted in no improvement in one patient. The severity of gastrointestinal bleeding and the excellent response to bephenium therapy was considered to be related to the species of hookworm involved.

Bephenium is recommended as the drug of choice in the treatment of severe hookworm disease during infancy.

Resumen

Se describen las historias clínicas de tres niños con infección masiva por *Ancylostoma duodenale.* Dos de los niños eran menores de un año de edad, el otro contaba 14 meses. Presentaban un cuadro clínico similar con anemia severa, evacuaciones sanguinolentas y eosinofilia. Fueron tratados con resultados excelentes con bephenium hydroxynaphthoate habiendo desaparecido la parasitosis. Tetrachloroetileno había sido usado anteriormente en uno de los pacientes sin obtener mejoría clínica. Se atribuyó la severidad de la sangría gastrointestinal y los resultados excelentes a la terapia con

bephenium a la especie de uncinaria envuelta.

Se recomienda el tratamiento con bephenium en casos de uncinariasis severa de la infancia.

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MINIMAL CEREBRAL DYSFUNCTION

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The Problem

The human brain is susceptible to damage by various deleterious agents. These include anoxia, ischemia, hypoglycemia, trauma, infectious agents and various toxic chemicals. When the exposure to the deleterious agent occurs in the already formed and developed brain, an acute or subacute clinical picture ensues which is the expression of the loss of function or areas of the brain affected. The clinician, thus localizes the lesion by the neurologic deficit. When the harmful agent acts on the immature or developing brain, however, the clinical results are different. If the harmful agent acts in the first few weeks of gestation, congenital defects of the brain, or indeed death of the embryo may ensue. If the harmful effects occur in the latter part of gestation, during the neonatal period, or in the early months of life, alterations may occur in the brain which may not be immediately apparent as a neurologic deficit simply because the structure or structures involved have not as yet developed function. Thus, this static (non progressive) lesion will be responsible for the future development of a slowly developing, on occassions, apparently progressive, neurologic picture which will depend on the extent of the damage, the location, the stage of the development of the brain, and the way in which the damaged area interferes with the development of non-involved structures.

In this fashion damage to the developing brain may result in mental retardation, the cerebral palsies, severe primary sensory loss, such as blindness or deafness, severe congenital aphasia, a severe seizure disorder, or any combination of the above.

When the damage is more subtle, however, a clinical picture may emerge which may be extremely puzzling to parents and to the child's physician.

In the past, children with this type of clinical picture have been seen and various diagnoses have been made, including organic brain disease, chronic brain syndrome, "brain damaged child", Hyperkinetic Behavior Syndrome, Character Impulse Disorder, Dyplexia, Primary Reading Retardation, Specific Learning Disability, and Clumsy Child Syndrome. As can be seen by the various diagnoses the symptoms may differ from child to child.

Since 1963 efforts to study this problem, define the syndrome, and establish a uniform nomenclature have been taking place at high levels. The term Minimal Brain Dysfunction has been adopted as the most appropriate and the syndrome has been defined as "children of near average, average, or above average general intelligence with

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certain learning or behavioral disabilities, which are associated with deviations of function of the central nervous system. These deviations may manifest themselves by various combinations of impairment in perception, conceptualization, language, memory, and control of attention, impulse or motor function (1)."

The most frequently encountered symptoms are as follows:

1. Those which have been described in the past as the Hyperkinetic Impulse Disorder:
   a) hyperkinesis
   b) short attention span
   c) impulsivity - poor judgement
   d) low frustration threshold
2. Learning difficulties
   a) in reading
   b) in arithmetic
   c) in spelling
   d) poor printing, writing and drawing ability
   e) poor ability for abstract thinking
3. Disorders of motor function
   a) delayed motor milestones
   b) general clumsiness or awkwardness
   c) frequent tics and grimaces
   d) frequent athetoid, choreiform, tremulous or rigid movement of hands
4. Disorders of speech and hearing

These children show little if any "hard" neurologic sings; but frequent, minor "soft" signs; such as:

a) reflex assymetry
b) mild visual or hearing impairment
c) strabismus
d) jerky eye movements
e) mixed laterality (right-handed and left-footed, etc.)
f) poor fine visual-motor coordination
g) impaired discrimination of size, right-left, up-down
h) impaired tactile discrimination
i) poor spatial orientation
j) impaired orientation in time
k) distorted concept of body image
l) impaired judgement of distance
m) impaired discrimination of part-whole
n) frequent perceptual reversals in reading and in writing letters and numbers
o) poor perceptual integration

Performance of these children in psychological tests is characteristic:

1. scatter - achievement low in some areas, high in others
2. below mental age level in drawing tests
3. poor in drawing geometric figures
4. poor performance on block designs, form boards, etc.

In the clinical evaluation of these children one of the difficulties encountered is the separation of the "primary" (organic) symptoms directly due to the impairment of function of the central nervous system, from the "secondary" (functional) symptoms due to the emotional effects of perpetual frustation, rejection and disapproval. In many cases the normal parent-child relationship is severely disturbed resulting in abnormal mood and affect, and interfering with the proper social maturation. Indeed, the prognosis of these children may depend to a very large extent on the severity of

the emotional overlay, and how the emotional problems are handled.

The Proposed Solution

The proper identification of children with minimal brain dysfunction, the diagnostic evaluation, and the treatment is a job which is extremely difficult to carry out by one professional under the present system, be he a physician, a psychologist or an educator.

There is a great need for the establishment of community centers where the job can be carried out by a team which should include pediatricians, neurologists, psychiatrists, psychologists, educators and social workers, equipped with the proper tools, and assisted by the proper technical personnel.

A child with minimal brain dysfunction would be referred to such a center, where he would receive a medical, psychologic, language and educational evaluation. Efforts would be made to identify:

1) Etiology
2) Nature of the primary handicap (deficit in perception, motor, function, integration, etc.)
3) Nature of emotional problems of child and parents

Treatment could then be planned and executed along the following lines:

1) Drug therapy (Ritalin®, dextroamphetamine, tranquilizers for impulse disorders, etc.)
2) Remedial education, speech therapy, etc.
3) Psychiatric treatment and counseling to child and parents

The establishment of a center such as outlined above, would result in the salvage of a large number of the citizens of tomorrow. The moneys spent in the development of such a center would be insignificant compared to the cost to the community of wasted education, inefficient vocational training and the maintenance of a large number of unemployed, uneducated psychiatric cripples and social outcasts.

Summary

Some of the author's ideas on the pathogenesis of brain damage in general, and minimal brain damage in particular are presented. The diagnostic criteria of the syndrome of minimal brain dysfunction is discussed, including common presenting symptoms, and signs. A short proposal on how children with this syndrome may be managed is outlined.

Resumen

Este artículo presenta algunas de las ideas del autor sobre la patogénesis de daño cerebral en general, y en particular sobre el daño cerebral mínimo. Se discute el diagnóstico del síndrome de disfunción cerebral mínima y los síntomas y signos más frecuentes.

Se expone brevemente un plan para el cuidado de los niños con este síndrome.

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AGANGLIONIC MEGACOLON IN INFANCY

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It is impressive how difficult the diagnosis of aganglionic magacolon in early infancy is and the high mortality it carries in our community. The reasons for this are the general misconception as to the clinical picture and the lack of experience of the pediatrician, radiologist, pathologist and surgeon that are occasionally called to deal with this uncommon problem. The misconception as to the clinical picture comes from the emphasis that has been given to the symptomatology in patients that survive infancy. These children present the classical picture described by the Danish pediatrician, Hirschsprung, around 1880; namely constipation, abdominal distention from megacolon and malnutrition. In infants the picture is quite different as will be shown in our clinical material.

In Hirschsprung's original description, he laid emphasis on the morphological characteristics of the disease, mainly, a hugely dilated colon. Thus the name megacolon was coined. Unfortunately, this diverted the attention of investigators away from the real cause of this condition and for almost sixty years the disease remained a pathological puzzle and a therapeutic failure. Although the absence of ganglion cells from the wall of the colon mucosa had been noticed earlier (as far back as 1901) it was not until 1940 when Tiffin, Chandler and Faber (1) first suggested an etiological relationship between aganglionosis of the rectosigmoid and the entity known as megacolon.

In 1944 Ehrenpreis (2) did extensive research into the etiology of megacolon. He bordered the realms of truth when he described the cause of megacolon as a neuroanatomical mechanism which he failed to describe. It remained for Swenson and Newhauser (3) to finally present the etiology of the condition as we know it today. In a classical piece of clinical research they devised experiments in which they were able to measure the peristaltic waves in the colon by means of ballons attached to kymographs. These were performed in patients with normal colon, with known or suspected megacolon and those already treated for this condition. They were able to demonstrate that in patients with aganglionosis, the peristaltic wave was present in the aganglionic segment but was not effective. They also noted that patients with colostomy or more definitive surgical treatment had normal peristaltic activity in the previously diseased portion of colon. By means of surgical biopsies they were able to correlate the absence of ganglion cells with the levels of abnormal peristaltic patterns. At the same time, Newhauser (3)

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brought forth the description of the "transition segment", that is, the segment where the diseased colon turns normal. This was seen radiographically as a change in the caliber from the small contracted aganglionic segment to the dilated bowel with a normal complement of ganglion cells.

After these facts were known, great improvements in the diagnostic and therapeutic approach to megacolon were made. Swenson (3, 4, 5, 6) devised an operation by which the diseased or aganglionic segment was removed and an anastomosis was made from the proximal segment to the remaining portion of rectum. This operation was performed after the patient had a preliminary colostomy working for some time and the proximal colon wall had been given a chance to return to normal size and the patients weighed about 25 pounds. To date, this remains the treatment of choice in this condition and it is generally known as the pull through operation. Recently there have been several modifications of this procedure that permit earlier definitive operation and at times avoid a preliminary colostomy (7, 8).

Clinical Material

This report consists of 13 patients seen between 1961 and 1965 at the San Juan City Hospital, the University Hospital and private hospitals in San Juan. This does not represent all the cases seen at these institutions but merely cases with which one of the authors (E. M.) came in contact. Six patients were female and seven were males. All were full term birth. All patients seen after the first week were underweight. The data is summarized in tables I to VII.

TABLE I: TIME OF SYMPTOMS

Day	No.	Age (Days) Seen by Surgeon
Birth	4,	4, 4, 4, 30
2	2	2, 3
7	3	17, 23, 28
10	1	10
20	1	60
30	2	37, 30

TABLE II: CHIEF COMPLAINTS

Complaint	No.
Diarrhea	3
Constipation	3
Vomiting	6
Abdominal distention	1

Notice that most patients had the onset of symptoms within the first week of life. There was considerable delay between the onset of symptoms and the surgical consultation. The chief complaint was variable and there was constipation only in a minority. Abdominal distention was the only common denominator in these cases.

It was usually associated with symptoms of upper or lower gastrointestinal dysfunction.

Fifteen different diagnoses were made and only in three cases was the disease suspected on admission.

Colostomy was performed in 11 patients. Two patients were too ill and died before colostomy.

TABLE III: OTHER SYMPTOMS

Symptoms	No.
Diarrhea	6
Constipation	7
Vomiting	8
Abdominal Distention	12
Jaundice	1
Fever	1
Omphalitis	1

TABLE IV: ADMISSION DIAGNOSIS

Diagnoses	No.
Acute gastroenteritis	5
Intestinal obstruction	5
Failure to thrive	3
Sepsis	3
Hirschsprung's	3
Milk allergy	2
Pyloric obstruction	2
Paralytic ileus	2
Meconium ileus	2
Malnutrition	1
Urinary infection	1
Meningitis	1
Lues	1
Post maturity	1
Omphalitis	1

TABLE V: DIAGNOSTIC STUDIES

Studies	No.
Barium enema	9
Rectal biopsy	5
Upper GI Series	2

TABLE VI: LEVEL OF AGANGLIONOSIS

Level	No.
Mid colon	1
Recto-sigmoid	8
All colon	2
Unknown	2

TABLE VII: OUTCOME

Outcome	No.
Died prior to definitive diagnosis during or shortly after preliminary colostomy	7
Discharged with temporary colostomy	6
Had definitive surgery	3

Discussion

Aganglionic megacolon is a disease of the autonomic nervous system. There is absence of parasympathetic ganglion (1, 3, 4, 6, 9) cells from the bowel wall starting at the internal sphincter of the anus and extending proximally to the rectosigmoid area in 90% of the cases and to the mid transverse colon in 10% of the cases (7, 10). The whole colon is involved in 1%, and there are case reports of aganglionosis extending up along the small bowel. Ninety percent of cases are seen in females according to several authors. The incidences is between 1/1000 to 1/2000 live births. In Puerto Rico in 1964 there were 80,000 live births, of which, between 80 to 160 cases should have been seen. The neurologic deficit in the large bowel leads to a spastic segment which fails to transmit a coordinated peristaltic wave and act as a low partial intestinal obstruction. In infants, the signs and symptoms of such an obstruction are not clear-cut as can be seen from our cases. Ninety-two percent of normal babies pass meconium in the first 24 hours (11, 12, 13). Failure to do so should bring to mind the possibility of aganglionosis specially if there is distention of the abdomen and dramatic release of stool and gas after a rectal instrumentation, although this usually discourages further investigation.

The disease may take one of three courses depending on the degree of obstruction and the treatment instituted. *First,* it may proceed in the first six days of life to total obstruction with constipation, distention and vomiting which may require immediate colostomy. *Second,* from the first week to three months the patient may show the sequelae of a partial obstruction after the subsidence of the first episode of total obstruction. Depending on the vitality of the patient's colon and the awareness of the medical personnel, this cycle may repeat itself until the patient's colon becomes de-

compensated, obstructs, perforates or the patient develops a fatal enterocolitis due to increased putrefaction, colonic ulceration and irritation leading to diminished absorption and increased secretions from the gut (14, 15). Finally, peritonitis, sepsis and death occur. If the diagnosis is made during these episodes a colostomy is done *after* medical treatment directed at decompression by enemas and control of infection with antibiotics is carried out. In this phase, the mortality is 50%. It is reported that one half of patients with this disease will have this complication. It has been called *paradoxical diarrhea or enterocolitis of Hirschsprung* and it is not related to fecal impaction. *Third;* should the patient survive these multiple episodes for three to six months, the classical picture of constipation, abdominal distention, megacolon, malabsorption and underdevelopment appears. At this point the diagnosis is obvious.

Hirschsprung's disease is responsible for 25% of fatal cases of intestinal obstruction in the newborn. It equals meconium ileus, jejunoileal atresia and volvulus (10,11, 12). The presenting symptoms are similar. A high index of suspicion is needed and a lot of negative examinations will be made in order to save a few lives. It is apparent that aganglionic megacolon has to be suspected in any infant in which there is an unexplained gastrointestinal disturbance whether it be vomiting, constipation or diarrhea specially if it is accompanied by abdominal distention. It is well to remember that failure to pass stool in 24 hours or passage of only one stool in 24 hours may be a sign of constipation in the neonatal period. A careful history must be taken from the mother in an attempt to determine bowel habits from the very first day of life. The mother must be questioned if there was need to do rectal instrumentation or suppositories to provoke the first bowel movement, or if there was a delay in discharging the patient from the nursery for any reason. The physical examination should reveal abdominal distention with increased peristalsis, a tight rectum beyond the sphincter and the explosive release of gas and liquid after a rectal examination. All of these may be absent at the time of examination. Plain films of the abdomen reveal dilated small and large bowel which are usually difficult to differentiate.

A balloon should not be used during barium enema as is done in adults because this will obscure the area where the pathology is. The narrow segment is better seen on lateral films. It takes between 18 days and 5 weeks for a megacolon to develop (16, 17, 18, 19). A *megacolon* may be seen with a zone of transition to a small caliber at the aganglionic level; it may show a *microcolon* in total Hirschsprung's as in cases of meconium ileus and small bowel atresia; it may show a *normal* colon-this is quite compatible with the diagnosis of aganglionosis in the neonate. In delayed films taken at 24 hours after the enema, the patient with aganglionosis still shows barium residue. A barium enema may exclude malrotation with volvulus of the midgut.

Next comes rectal biopsy. This is done under general anesthesia and adequate help to procure a segment of rectal muscle. This procedure is not recommended in the desperately ill infant who would be better served by saline rectal irrigation, rectal dilatation and antibiotics.

In certain centers where there is proficiency with frozen section in the diagnosis of this condition, the colostomy is done at

the appropriate level once this level is established by multiple sections. In our environment, it is best to do a permanent section and then at a later date explore the abdomen for a colostomy.

A word of caution is in order. Infants are explored in the neonatal period with the diagnosis of intestinal obstruction. At operation, the surgeon finds a minimal to moderate small and large bowel gaseous distention and fails to recognize that this may represent aganglionosis and does not take a rectal biopsy or do a colostomy and assumes that the problem is that of paralytic ileus, bands or malrotation and closes the abdomen without a diagnosis and the patient goes on to die of the disease.

Once the diagnosis is certain, a colostomy is done as soon as the patient is in fairly good condition, in preparation for a Swenson's pull-through, or a modification of a pull-through may be done at once. The overall mortatily in infancy is 70% in the United States. In our series, the mortality so far is 54%. Since we have seen so few patients in relation to what we should have seen according to the reported incidence, it may mean that a lot of these infants die undiagnosed and this brings the mortality up. This theory is strengthened by the fact that we ran routine pathological sections of rectum on patients dying in our contagious disease ward of chronic gastroenteritis and found cases of unsuspected aganglionosis. Another reason is that we have seen an increased incidence since we have become aware of the clinical picture of aganglionosis in infancy.

Summary

Aganglionosis of the intestine in infancy does not give rise to clear characteristic clinical picture except for the presence of distention of the abdomen in a patient with either constipation, vomiting or diarrhea. This picture is quite different from Hirschsprung's in older children where there is chronic constipation, enlargement of the abdomen and malnutrition. The mortality is 70% in infants. The clinical picture and the management of our cases is discussed.

Resumen

La aganglionosis del intestino en el infante no tiene un cuadro clínico fijo ni claramente definido, y se manifiesta por la presencia de distención abdominal en un infante con estreñimiento, vómitos o diarrea. Este cuadro es muy diferente al del megacolon clásico en el niño o en el adulto en los cuales hay estreñimiento crónico, distensión abdominal y desnutrición. La mortalidad en los infantes es de 70%. Hemos presentado el análisis del cuadro clínico en nuestros casos y hemos discutido el manejo de la enfermedad.

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THE CONNECTIVE TISSUE DISORDERS:
The Mucopolysaccharidoses A Review

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Recent advances in the recognition of gene-determined disorders of mucopolysaccharide metabolism have made it possible to clarify the heterogeneity found in the Hurler's Syndrome and its variants. Knowledge of the intricate chemical structure of connective tissue is now sufficiently advanced to permit some interpretation of the pathogenesis of these diseases in terms of their biochemistry. This, added to the clinical, radiological and genetic characteristics of these diseases, has made a working classification possible. For a precise knowledge of the connective tissue disorders one must first understand the nature of a mucopolysaccharide.

Biochemistry

All higher organisms develop some type of extracellular material to act as a "bridge" between the highly specialized parenchymal cell and its blood stream. It is through this connective tissue that both nutrient and waste materials are exchanged. For simplicity one could think of this tissue as consisting of two cell types: the fibroblast and the mast cell; and, two distinct varieties of fibers: collagen and elastin, which are present in a ground substance of acid mucopolysaccharides.

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The acid mucopolysaccharides are a group of eight closely related yet specific substances composed of amino sugars, uronic acid and sulfate, closely bound by a small serine residue to a protein complex. Table I shows their specific composition.

The word mucopolysaccharide comes from the structural composition of a protein moeity joined to a repeating disaccharide unit. The manner of linkage of carbohydrate to protein is not yet completely defined, but as will be indicated below, may be of great importance as the region involved in the inborn error of metabolism. Due to the works of Muir (1) and Roden(2), it is now possible to present a schematic structure of a polysaccharide macromolecule (Figure 1).

With this as a basis, several theories (3,4) have been advanced to explain how the genetic error is translated into the symptom complex.

The most attractive hypothesis suggests that there is a defective binding of mucopolysaccharides in tissues. Several possibilities exist for the exact site of this abnormality. As shown above, two galactose and one xylose residues are interposed between the polysaccharide chain and the serine molecule. The defect may then be in the galactose, the xylose, or the serine binding. This will explain various polysaccharidoses as

TABLE I. MUCOPOLYSACCHARIDES OF CONNECTIVE TISSUE

Compound	Amino Sugar	Uronic Acid	Sulfate
Hyaluronic acid	Glucosamine	Glucuronic	0
Chondroitin	Galactosamine	Glucuronic	0
Chondroitin SO_4 A	Galactosamine	Glucuronic	1
Chondroitin SO_4 B	Galactosamine	Glucuronic	1
Chondroitin SO_4 C	Galactosamine	Glucuronic	1
Keratosulfate	Glucosamine	Galactose	1
Heparin	Glucosamine	Glucuronic, Iduronic	3
Heparin monosulfuric acid	Glucosamine	Glucuronic	1

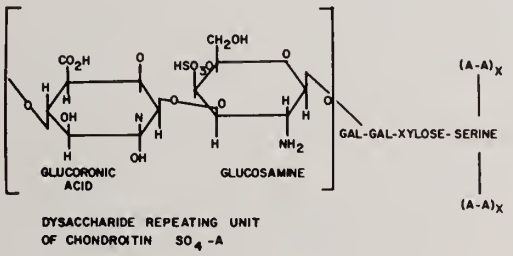


Fig. 1: Mucopolysaccharide pattern.

defects in different critical regions of binding.

An alternative explanation is to propose an abnormal regulation of polysaccharide or protein synthesis. Therefore, if the macromolecule that comprises the structural component of connective tissue is not formed, the polysaccharide chains will diffuse out to be deposited in organs throughout the body or to be excreted in the urine (5).

Whatever the ultimate mechanisms are, they cause the metabolic derangements responsible for the various clinical syndromes which are to follow.

Clinical Features

The method of classification proposed by McKusick (6) will be used since it is the least confusing (Table II).

Hurler's Syndrome

Historically, this is the earliest prototype of the mucopolysaccharidoses to be recognized (7). Typical patients bear a strinking resemblance to one another. They are characterized by moderate but asymmetrical dwarfism, macrocephaly usually with scaphocephaly, grotesque facial appearance with macroglossia, widely spaced teeth, kyphosis, lumbar gibbus, hepatosplenomegaly, cardiac abnormality, protuberant abdomen and profound progressive mental deterioration. The upper extremities are broad and short with stiff joints and claw-like hands.

Progressive clouding of the cornea occurs in all cases; and this, accompanied by radiologic changes in the skeleton, more or less typical of this specific entity, should suggest the diagnosis which is then proven by finding elevated levels of chondroitin sulfate B and heparitin sulfate in the urine. Death usually occurs by the first decade of life.

Hunter's Syndrome

In all respects, Hunter's Syndrome is quite similar but less severe than mucopolysaccharidosis I. Patients usually survive into adulhood, with the oldest known case dying at the age of 60 years (6). Leading features are: disproportionate dwarfism, claw-like hands, stiff joints, and "gargoyle" facies. However, lumbar gibbus and clinical corneal opacities do not occur. Instead, conduction deafness and heart disease — en-

TABLE II. CLASSIFICATION OF THE MUCOPOLYSACCHARIDOSES

Type	Clinical	Biochemistry	Inheritance
MPS I Hurler's Syndrome	Normal at birth but progressive severe mental retardation; severe bone deformities; gross corneal opacities and early death	Chondroitin SO_4B and heparitin SO_4	Autosomal recessive
MPS II Hunter's Syndrome	No clinical clouding of cornea; slower mental deterioration; milder course	Chondroitin SO_4B and heparitin SO_4	Sex-linked (male) recessive
MPS III San Filippo's Syndrome	Severe progressive mental retardation; somatic changes and bone deformities; no corneal clouding	Heparitin SO_4	Autosomal recessive
MPS IV Morquio's Syndrome	Corneal opacities dwarfism; characteristic skeletal and dental abnormalities; possible normal intelligence	Keratosulfate	Autosomal recessive
MPS V Scheie's Syndrome	Dense corneal opacities in infancy; normal height and intellect; mild bone changes	Chondroitin SO_4B	Autosomal recessive
MPS VI Maroteaux-Lamy's Syndrome	Moderate bone deformities; gross corneal clouding; no intellectual impairment	Chondroitin SO_4B	Autosomal recessive
MPS VII Dyggve's Syndrome	Severe mental retardation; no corneal opacities; characteristic bone deformity	(?) Modified hyaluronic acid chondroitin SO,B	Autosomal recessive

docardial, myocardial, pericardial and coronary — occurs more frequentely. Chondroitin sulfate B and heparitin sulfate are found in the urine of affected patients. Some investigators (8) claim to have found a quantitative difference in the excretion of these substances in Hurler's and Hunters's Syndromes but others (5,6) do not bear this out.

San Filippo's Syndrome

In 1963 San Filippo *et al* (9), described eight children with mild clinical deformity but progressive mental deterioration. In common with the above, they have slight to moderate dwarfism, hepatosplenomegaly, stiff joints and claw-like hands. No gross corneal clouding occured; although, one of the patients subjected to slit lamp examination had some corneal changes. In their urine only heparitin sulfate was excreted in excess. These children live well into the second decade of life.

Morquio's Syndrome

Since first described in 1929, by Morquio (10) and Braislsford (11) independently of each other, this syndrome has been a waste basket for many ill-defined skeletal disorders. It has not been until recently that with better follow up and biochemical methods, that the complete clinical entity

has been defined. During the first two years of life the patients may be impossible to differentiate from Hurler's Syndrome on clinical grounds alone. Later on, the characteristic kyphosis of the spine and flat vertebral bodies occur. A major point in differentiation is the absence of mental retardation. Most children affected die by the beginning of the second decade of life but those that survive longer then have to cope with progressive corneal opacities, deafness and hepatosplenomegaly. Keratosulfate in abnormal amounts is excreted in the urine (Figure 2).

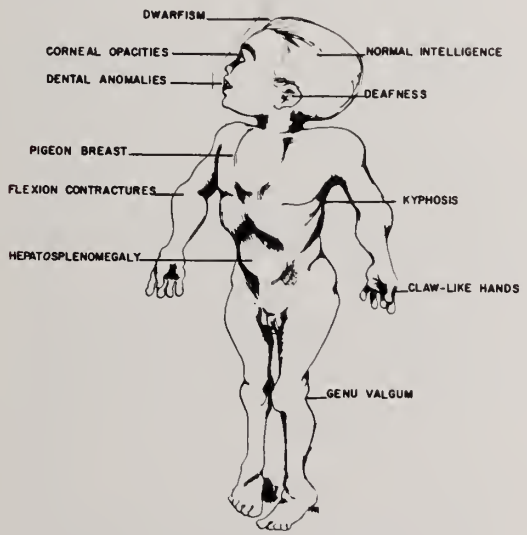


Fig 2: Morquio's syndrome.

Scheie's Syndrome

In 1962, Scheie (12) and his associates, reported on a group of patients who had extensive corneal opacities, normal to superior intelligence but who varied widely in respect to the presence of other manifestations of Hurler's syndrome. Stature is normal to low normal. Stiff joints, hirsutism, claw-like hands and retinitis pigmentosa occur progressively with advancing age, Whether life expectancy decreases has yet to be proven. Terry and Linker (8) examined the urine of two of Scheie's patients and found both chondroitin sulfate B and heparitin sulfate. McKusick *et al* (6) analyzed the urine of another of Scherie's patients and several other patients whom they considered to have the same clinical picture and found only chondroitin sulfate B. There is a question then, as to whether Scheie's patients represent more than one syndrome.

Maroteaux-Lamy's Syndrome

These are children with bone changes on roentgenograms similar to those observed in patients with the Hunter-Hurler's syndrome (13). However, the clinical picture of dwarfism, genu valgum, lumbar kyphosis and pectus carinatum are more suggestive of Morquio's disease. Corneal clouding is severe. Intelligence is unaffected. Urine analysis establishes the diagnosis.

Dyggve's Syndrome

First described in Greenland (14), these patients have intermediate bone changes similar but not equal to those in Mucopolysaccharidoses I and II. The patients had red hair, were mentally retarded and excreted some form of hyaluronic acid in the urine. Further work is necessary to see if these patients described by Hobaek (15) and Harris (16) belong in this category.

There is hardly any doubt that the number of inborn errors of metabolism due to abnormalities in mucopolysaccharide chemistry will continue to rise. This, of course, will not be due to an increase incidence but rather to a greater awareness and better diagnostic methods.

Rarely does a month go by in which the medical literature does not present us with new cases to consider. By finding

abnormal mucopolysaccharides in the urine of patients, the molecular biologist has given us a common denominator bringing together what used to be thought of as unrelated bone and/or neurological aberrancies.

What is still needed is a further understanding of the molecular physiology responsible for the gross signs and symptoms which we see in these unfortunate children. Until this is known, successful treatment will have to wait.

Acknowledgment

I want to acknowledge the encouragement and helpful suggestions of Dr. John Kirkpatrick, Chief of the Radiology Department, St. Christopher's Hospital for Children, Philadelphia, Pa., in the preparation of this paper.

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EDITORIAL

NUEVOS HORIZONTES EN LA EDUCACION MEDICA

Los programas de estudio de las escuelas de medicina norteamericanas que por muchas décadas fueron instrumentos finamente ajustados a las exigencias de la época, se enfrentan hoy con cambios fundamentales en la naturaleza y extensión de los conocimientos médicos y en la sociedad que éstos están llamados a servir. Por consecuencia las escuelas de medicina, para llenar a plenitud su cometido, tienen que variar su enfoque y sus métodos para adaptarlos a la nueva situación.

Está en pie un gran movimiento de reforma en la enseñanza de la Medicina y la mayoría de las escuelas está revisando sus currículos. Uno de los factores más importantes que impulsan la reforma es el prodigioso aumento en el caudal de conocimientos a la disposición del médico. Sería inútil pretender enseñar todas estas materias en los cuatro años del currículo tradicional, materias que no se podrían aprender aún en una vida entera. Por lo tanto se impone el utilizar un cedazo más fino para seleccionar con sagaz criterio e impartir con depurada eficiencia la información y los conceptos fundamentales. Hay que aprovechar el tiempo y la ocasión propicia, entrelazar lógicamente las materias, e inspirar y estimular el mayor esfuerzo productivo de parte del estudiante. En otras palabras, hay que refinar los métodos pedagógicos. Es obvio que en este refinamiento entran otros factores además de la reforma del currículo, que no es nada más que un medio hacia un fin. Los métodos a que me refiero, que sería prolijo enumerar, requieren amplio dominio de la materia a enseñar, plena utilización de los medios modernos de comunicación, buena técnica pedagógica, intuición, sentido común y otros imponderables

Estaríamos satisfechos con formar un médico que comprenda los principios básicos de la medicina, que conozca los métodos a utilizarse y su aplicación inteligente, que tenga el interés, el deseo, y los buenos hábitos de análisis y de estudio para continuar aprendiendo y mejorándose durante su carrera profesional, y que en medio de todas las presiones, conserve su orientación humanitaria.

Comprendo que todo esto en su plenitud sería difícil de conseguir en el estudiante promedio, que es el que más nos interesa, pero no por eso deja de ser nuestra aspiración.

Otra de las consecuencias de la explosión de conocimientos es la de que acentúa y hace casi obligatorio lo que ya existía como una tendencia hacia la especialización. Del 80 al 85% de los médicos graduados recientemente se especializan porque ya no pueden dominar, a su satisfacción y a la satisfacción del público que lo exige, más de un sector de la medicina. Ya las escuelas de medicina no pueden pretender preparar médicos para hacerlo todo y hacerlo razonablemente bien dentro de las normas prevalecientes. Aún la práctica general conlleva cierta especialización y ciertas limitaciones. Por lo tanto los nuevos programas docentes deben proveer, con énfasis adecuado, los conocimientos básicos que todos los médicos, la mayoría de ellos futuros especialistas, necesitan en común. Pero aquellas materias que con lujo de detalles sólo son esenciales para un grupo de especialistas no deben ser obligatorias para todos los estudiantes. Por ejemplo, antes se enseñaba la anatomía estructural hasta el más mínimo detalle porque se suponía que todos los médicos debían estar preparados para emprender intervenciones quirúrgicas, para mayor asombro, en cualquier región del cuerpo. Este concepto ha cambiado, naturalmente, aún entre los más fervientes anatomistas.

No debemos pretender y menos aún exigir que los estudiantes de medicina se lo aprendan todo por igual: hay que reconocer que hay variedad de intereses y variedad de propósitos. Los currículos del futuro deben deslindar, por lo menos, ciertos campos amplios de actividad tales como medicina de adultos o medicina de niños, investigación y carreras académicas, ciencias básicas o ciencias clínicas médicas o quirúrgicas, ciencias de la conducta, medicina de la comunidad u otras divisiones en cierto sentido generales. La especialización específica debe desarrollarse más tarde. Lo ideal sería, como apuntó el Dr. Oliver Cope, un currículo para cada individuo, algo imposible, pero que enfatiza la conveniencia de individualizar la docencia proveyendo orientación personal, suficiente tiempo libre, y oportunidad substancial para actividades electivas.

Hemos dicho antes que la especialización es en parte consecuencia de la extensión de los conocimientos médicos y lo complicado de las técnicas que se han ido desarrollando. También es una consecuencia de la demanda de la comunidad que legítimamente exige servicios médicos de alta calidad, mejor distribuidos. Hay que atender esta demanda porque la medicina no funciona en el vacío sino dentro del marco de una sociedad a la cual está intimamente ligada. Las escuelas de medicina modernas cooperan en la búsqueda de mejores sistemas de servicios médicos. La meta de todo aprendizaje, de toda investigación y de todo esfuerzo personal y colectivo sigue siendo la de servir mejor a la comunidad.

Otras consideraciones que se están tomando en cuenta al tratar de diseñar nuevos currículos o reformar los antiguos es la necesidad de introducir temprano en los estudios los nuevos conceptos sobre la estructura y el funcionamiento íntimo de las células. La medicina moderna se basa en estos conceptos. Hay que enfocarlos bien y relacionarlos con el funcionamiento del ser humano y sus reacciones ante la enfermedad. Partiendo de esta base, un concepto dinámico del crecimiento y desarrollo psíquico y somático del hombre dentro de su ambiente nos ayudaría a comprender sus problemas para así poder aliviarlos.

Para poder mantener un punto de vista amplio hay que correlacionar las materias a enseñarse haciendo caso omiso de las barreras creadas artificialmente por las excrecencias de la especialización y las estructuras departamentales. Para mí personalmente el mejor sistema curricular se podría describir como una "interdigitación", o sea a la manera de dos manos entrelazadas, de modo que las ciencias clínicas se empiecen a enseñar en forma gradual y progresiva desde los comienzos de los estudios y las ciencias básicas continúen su influencia a través de los años clínicos. Las ventajas de este sistema son obvias sobre todo en lo que respecta a la motivación de los estudiantes. El aprendizaje sería menos penoso y más sólido, más significativo, y tendería a evitar el divorcio entre ciencia y arte que a veces persiste en el médico ya formado.

Para una enseñanza productiva es esencial que exista la integración de las enseñanzas clínicas y básicas y la más estrecha colaboración entre las disciplinas en ambos campos.

El concepto de inter-relación dinámica se podría también aplicar a las relaciones entre la escuela de medicina y los estudios preparatorios que la preceden y los estudios post-graduados, internados, residencias, etc. que la siguen. En estos casos debe haber hilación pero no un empate firme y rígido que crearía un profesional estereotipado. Sobre todo en los estudios pre-médicos hay que evitar la excesiva concentración en las ciencias en detrimento de la preparación general del individuo que más bien la imprimen las llamadas humanidades. El médico debe ser antes que nada una persona culta, como la define Ortega y Gasset. Debe comprender y amar a la humanidad y debe estar listo para participar significativamente en el campo de las ideas y de la acción, en la sociedad en que convive.

No queremos olvidar en la discusión de los currículos al objeto principal y el móvil de todos los programas: el estudiante. El buen maestro debe comprender al estudiante, guiarlo por la palabra y por la acción, que es el buen ejemplo, y sobre todo estimularlo para que tome parte activa en su propio entrenamiento.

Del intercambio surge la chispa. En el estudiante hay que incubar el hábito de discutir y cuestionar las premisas presentadas, hay que estimular su curiosidad y su interés en buscar más información, y facilitarle los métodos para conseguirla y aquilatarla.

El investigador, parte esencial de toda facultad de medicina, contribuye a la preparación del estudiante ayudándole a afinar su criterio, estimulándolo a buscar nuevas soluciones y demostrándole la productividad del método y la disciplina.

El currículo ideal es flexible y provee tiempo libre, asignaturas electivas y otras oportunidades. Lo importante en la labor del maestro es el formar la aptitud del estudiante para pensar, estudiar y aprender por su cuenta como tendrá que hacerlo el resto de su vida.

La mayoría de los educadores médicos están de acuerdo con los conceptos vertidos. Sin embargo pocas escuelas han reformado su currículo radicalmente pero casi todas han tomado pasos en la dirección señalada. Los cambios significativos han afectado principalmente las ciencias básicas. Generalmente los funda mentos se presentan en la forma clásica departamental, pero el grueso de la enseñanza consiste en el estudio integral de los varios sistemas con la participación conjunta de varios departamentos. En la enseñanza clínica ha habido un cambio en el enfoque y se ha establecido una mayor correlación interdisciplinaria, y se ha liberado una gran parte del cuarto año para actividades electivas.

Hemos discutido en síntesis las ideas que orientan a nuestras escuelas de medicina en su esfuerzo por adaptar su currículo a los cambios en la naturaleza y cuantía de los conocimientos médicos y a las demandas legítimas de una sociedad en continuo desarrollo. Comprendemos que el reformar la distribución y la secuencia de las horas de aprendizaje no es decisivo y que lo verdaderamente importante es el modernizar los métodos de enseñanza dentro de un currículo funcional. Hemos querido recalcar que más allá de todos los sistemas docentes juegan un papel decisivo las relaciones entre el maestro y el estudiante. Este factor, por lo humano, es muy difícil de analizar. Recordemos maestros y discípulos que más importante que el caudal de conocimientos que se imparta o que se adquiera es la formación de una persona.

Hemos enfatizado que a través de toda su preparación el médico debe atesorar su cultura y conservar su humanidad, para poder cumplir su misión abarcadora con algo más que ciencia y tecnología.

Antonio Ortiz, M. D.

ACTUALIDADES MEDICAS

Suicide in the United States, 1950-1964

Cause-of-death statistics for 1964 show an average of 56 suicides committed daily in the United States. The 20,588 reported suicides represented about 1 percent of all deaths occurring in the United States during the year. The rate was 10.8 per 100,000 population. Since 1900, the suicide rate has ranged from a high of 17.4 in 1932 to a low of 9.8 in 1957. It has not exceeded 12.0 per 100,000 since 1941.

Suicide has been among the 12 leading causes of death for the past 10 years. It has been even more prominent among teenagers and young adults. It ranked fourth in 1964 for age groups 15-24 and 25-44 years. (Of course, this high rank for these age groups reflects the smaller number of deaths from most other causes, as well as the actual number of suicides.) Although suicide was of less importance as a cause of death in the upper age groups, where deaths from other causes are more numerous, it remained one of the 10 leading causes through the age group 45-64 years.

Suicide is suspected of being grossly understated in the statistics based on cause-of-death certification. A general reluctance to admit suicidal intent of friends and relatives and difficulties in recognizing it under certain circumstances undoubtedly result in underreporting. Various estimates have been made of the actual occurrence of suicide, some indicating that it is as much as twice the reported figure. In addition, many attempts at suicide are unsuccessful. Although there are no national statistics on this topic, at least one study (Farberow and Shneidman, *The Cry for Help*) places the ratio of unsuccessful attempts at suicide to committed suicide in the neighborhood of 8 to 1.

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Firearms and explosives are more frequently used for committing suicide than any other means of injury. This category, comprised principally of deaths attributed to self-inflicted gunshot wounds, accounted for 48 percent of all suicides in 1964. Hanging and strangulation was the next most frequent means and accounted for about 15 percent of the total suicides, About 12 percent were from poisoning by analgesic and soporific substances. Nearly three-fourths of these involved the use of barbituric acid and its derivatives. The only other category which accounted for more than 10 percent of the suicides in 1964 was "poisoning by other gases." Of these, 9 out of 10 involved motor vehicle exhaust gas.

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The choice of a way to commit suicide varies by sex. For instance, analgesic and soporific substances were used by only 6 percent of males committing suicide, compared with 30 percent of females. Except for suicides from poisoning by other gases (which includes motor vehicle exhaust gases), poisonous substances were used by a greater percentage of females than of males. Also, a greater percentage of females

drowned themselves. Firearms and explosives accounted for 56 percent of all suicides for males, but only 25 percent of those for females. Other means of suicide varied by sex but the differences were negligible.

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Suicides are more frequent in the spring than in any other season. When the number of suicides per day by each month is computed (to eliminate length of month as a factor influencing the number of suicides for a given month), March, April, and May have the highest averages. April had the highest daily average in 10 of the 15 years from 1950 through 1964, May and June the highest for 2 years, and March for 1 year. The months with the lowest number of suicides per day are the winter months — November, December and January. An average for the 15 years shows the number of suicides ranging from 46 per day for December to 54 per day for April.

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Suicides occur much more frequently among males than among females. The rate for males was almost three times that for females in 1964. Seventy-three percent of the persons committing suicide in the United States in that year were males. In 1950 this percentage was 78 percent. There is evidence, however, that a much larger proportion of the unsuccessful attempts at suicide are made by women. In a study by Farberow and Shneidman (reported in *The Cry for Help*), based on statistics for Los Angeles County in 1957, 70 percent of the suicides were committed by males while almost 70 percent of the persons unsuccessfully attempting suicide were females, Other studies support these percentages.

Suicide also occurs more frequently in the white population than in the nonwhite. In 1964, the ratio between rates for white and nonwhite persons was 2 to 1.

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Of the States, Nevada had the highest average annual suicide rate for the 3-year period of 1959-61. The other western States also had high rates. The suicide rates for the southern States, with the exceptions of Virginia and Florida, were among the lowest in the United States. This is also true when the rates are adjusted for age.

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The age-specific suicide rates (1959-61) for married persons were lower than those for the single, widowed or divorced. This was true of all age groups except for the 15-19, 80-84, and the 85-years-and-over groups. Divorced persons showed the highest suicide rates—from three to five times the rates for married persons under 65 and from two to three times greater in age groups over 65. The rates for widowed persons were eight times those for married persons at ages 20-24, but this ratio gradually declined with age and the rates were almost identical after reaching age 60. Suicide rates for single persons in most age groups ranged from 1½ to 2½ times those for married persons.

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Homicide in the United States, 1950-1964*

Nearly 123,000 deaths were attributed to homicide in the years 1950-64. The number has risen almost every year, from 7,942 deaths in 1950 to 9,814 deaths in 1964. The rate has fluctuated between 4.5 and 5.3 per 100,000 persons during this period.

** Reprinted from Vital and Health Stantics, National Center for Health Statistics, Series 20, Nos. 5 and 6.*

Despite the low overall mortality as compared with accidents or suicides, homicide remains a leading cause of death in certain segments of the population. In 1964 it was the seventh largest cause for nonwhite males in the United States. It ranked second for both nonwhite males and nonwhite females aged 15-24 years.

Over the years, homicide appears to have gone through three stages. From the turn of the century, when only one homicide per 100,000 population was recorded, the rate rose to a peak of 9.8 in 1933. During the next 22 years, the rate dropped (with one upturn in 1945 and 1946) to 4.5 in 1955. Since 1955, there has been a slight up-turn, to 5.1 per 100,000 persons in 1964.

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The homicide rate among females has remained essentially unchanged at 2.3 or 2.4 deaths per 100,000 for most years since 1950. This annual rate is about one-third as high as that for males, who experienced about 7 or 8 deaths per 100,000 persons during the same period. In the latest years, 1962 through 1964, the rate for males has risen slightly, but not beyond the level that prevailed in the early 1950's.

The homicide rate for the white population leveled off at 2 or 3 deaths per 100,000 population after 1950. The rate for the nonwhite persons continued declining through 1961; in 1950 it stood at 28 deaths per 100,000—11 times the average among white persons. By 1961, the rate had fallen to 21, which was still eight times the rate of the white population. In the last 3 years, 1962 through 1964, the rate for nonwhite persons increased again.

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Adults 25-44 years of age accounted for nearly half of the homicides, with a rate of 9.8 per 100,000 population in 1964. This was the highest rate of adult homicide in 15 years, about 5 percent above the level for 1950, and 21 percent above that for 1958, the year with the lowest rate since 1950. At ages above 45, the rate tapered off to 3 homicides per 100,000 for those 65 years or more.

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The killing of infants under 1 year of age—infanticide—has been increasing since 1957. Although the number of infant homicides accounted for only 2.2 percent of the total homicides in 1964, the rate of 5.4 deaths per 100,000 population was higher than that for all persons aged 55 years and over. The 74 percent increase from 3.1 in 1957 placed infanticide in 1964 at the highest level recorded since 1945.

Homicide rates for persons 15 years of age and over are highest for the divorced and lowest for the widowed. Comparisons of homicide rates among the marital status groups are affected by the differing age compositions of these groups. Age-adjusted rates for 1959-61 (3-year average) by marital status, adjusted to the 1940 population aged 15 and over, showed the lowest rate for married persons and the next lowest for single.

Mumps Virus Vaccine •

A live attenuated mumps virus vaccine will be licensed for use in December 1967 or early in January 1968. Studies to date have indicated that the vaccine has the following characteristics:

1. It has not caused clinical reactions.
2. It has been antigenic, inducing an

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antibody response in over 90 per cent of susceptible individuals.

3. Transmission to susceptible contacts has not been observed.
4. The neutralizing antibody levels have been lower than those observed following natural mumps infection.
5. Protection against mumps has been observed in children who were exposed 8 months to 2 years after vaccination.

Until more definitive information is available with respect to duration of immunity, the Committee does not recommend the routine use of mumps vaccine for all infants and children. In view of the potential benefits of the vaccine, its use for the following special groups of individuals should be considered if they have not had clinical mumps:

1. Boys who are approaching puberty.
2. Adolescent and adult males.
3. Children living in closed institutions, perhaps in summer camps, or under other similar epidemiological circumstances.

Inactivated mumps vaccine or mumps immune globulin are no longer recommended for susceptible adult males who have been exposed to a person with mumps. There is insufficient data as yet on which to judge the possible value of live attenuated mumps vaccine in preventing disease following exposure.

Chemoprophylaxis for the Prevention of Tuberculosis

Approved May 21, 1967 by the NTA Committee for the Guidance of the Tuberculosis Program and the American Thoracic Society Executive Committee. Accepted by the NTA Board of Directors on May 27, 1967.

Endorsed by the Ohio State Medical Association and the Ohio Department of Health.

Since the publication in February, 1965, of the statement by the American Thoracic Society Committee on Therapy entitled "Preventive Treatment in Tuberculosis," the indications for chemoprophylaxis have widened. The National Tuberculosis Association Committee for the Guidance of the Tuberculosis Program established an Ad Hoc Committee on Chemoprophpylaxis with representation from the ATS Commitee on Therapy, the ATS Committee on Respiratory Diseases in Children, the United States Public Health Service, and the NTA Committee for the Guidance of the Tuberculosis Program, which prepared the following statement:

Antimicrobial drugs, which have revolutionized the therapy of tuberculosis, can also be effectively used in chemoprophylaxis, the prevention of disease in the infected individual. Chemoprophylaxis presumably acts by diminishing the bacterial population in "healed" or invisible lesions of the person taking the drug. It is in reality treatment of infection and prevents clinical disease from developing or relapsing.

A substantial and growing body of scientific data testifies to the value of anti-tuberculosis drugs in prevention of clinical tuberculosis. The extensive trials conducted by the United States Public Health Service show a consistent reduction of morbidity in treated groups; it seems reasonable to expect that chemoprophylaxis can reduce future morbidity from tuberculosis in these high risk groups by some 50 to 75 per cent. The extensive use of chemoprophylaxis now, would likely reduce by 300,000 the total number of cases in the United States in the next 15 years.

Chemoprophylaxis can be instituted on a widespread basis through two major means.

1. The family physician, pediatrician or internist can institute chemoprophylaxis on an individual basis in patients who have a high risk of developing active tuberculosis.
2. Community agencies can work with the high risk groups that can be approached through a public health program. In many instances, these persons are already known to health departments and their names are in the files of closed cases and in the reports from screening programs.

Drugs used in Chemoprophylaxis

A single drug, isoniazid, is generally used for chemoprophylaxis in a dosage of 300 mg. per day for adults and 10 mg. per kilogram body weight per day for children, not to exceed 300 mg. per day, to be administered in a single daily dose for a period of twelve months.

There are virtually no side effects. The toxicity to this drug is low, apparent in only 0.2 to 0.4 per cent of those taking the drug, and it is easily reversible. Follow-up studies for periods of up to fifteen years of groups of people who have been treated with isoniazid have revealed no evidence of long term deleterious effects from its use. Isoniazid is also inexpensive.

Motivation of Patient

With adequate motivation, most patients will accept and stay on drugs for the full course. Enthusiasm and encouragement by the physician, nurse and other health personnel involved are key factors. At the beginning of a course of prophylaxis, the physician should take time with the patient to establish understanding and motivation. Subsequently there should be regular visits with the public health nurse either in the clinic or at home to reinforce the physician's teaching. Patients should be helped to develop their own systems of reminders to take drugs daily. In addition, maintaining the drug schedule should be made easier for patients by removing obstacles such as difficulties in getting to clinics for follow-up visits or in obtaining drug refills.

Persons Recommended for Chemoprophylaxis

Every positive reactor is at some risk of developing active disease. Thus, any person found to have a reaction of 10 mm. or more to the Mantoux test using 5 TU of PPD should receive chemoprophylaxis whenever he is identified.

Since in the immediate future it is not practical to test and treat the entire population of positive reactors, priorities must be set for public health programs taking into consideration the relative risk of developing active disease, the opportunities of infecting others particularly children, and the resources available in the community. The total cost must also be taken into account.

For certain groups, chemoprophylaxis is mandatory. These groups include certain inactive cases, certain special clinical situations; contacts, converters and positive reactors among young children and adolescents.

Persons with Inactive Tuberculosis

First priority for chemoprophylaxis should be given to persons with inactive tuberculosis. These include:

1. Ex-patients; persons who have had active tuberculosis and had no drug

therapy or had inadequate drug therapy.

2. Persons with X-ray findings consistent with healed adult-type pulmonary tuberculosis and a positive tuberculin test. (Some persons over age 55 may be negative to 5 TU of PPD and a larger dose of tuberculin may be necessary to elicit a reaction.)

It is essential to exclude active disease in these groups by bacteriological examinations, comparison with previous radiological findings, and other investigations, because people with active disease require more intensive drug treatment.

The rate of reactivation among these inactive cases is between 0.5 per cent and 2.0 per cent per annum. Many of these cases are known to health departments. It is a worthwhile program to review the records of inactive cases, and recall them for assessment of the need for chemoprophylaxis. Such a program directed towards a well delineated group would be more practical than surveying the whole community.

Special Clinical Situations

A person with a positive tuberculin test is in danger of activation or reactivation of tuberculosis in certain clinical situations. Such a person should receive chemoprophylaxis whether or not he has been treated with isoniazid before: if he is placed on corticosteroid treatment, if he undergoes gastrectomy, if he has reticuloendothelial disease such as leukemia or Hodgkin's disease, or if he has a period of instability of severe diabetes. In the case of a pregnant woman who has inactive tuberculosis previously untreated with chemotherapy, or who has X-ray shadows consistent with inactive tuberculosis, chemoprophylaxis should be started in the last trimester and continued for a year.

When children with a positive tuberculin reaction develop measles or whooping cough they should receive eight weeks of chemoprophylaxis if they have been treated before; the course of chemoprophylaxis should be extended to 12 months if they have not received previous treatment.

Contacts

Contacts of recently discovered new active and reactivated cases of tuberculosis show a high incidence of this disease. Contacts should be examined and those diagnosed among the contacts as having tuberculosis should be reported and treated.

All household contacts of a reported active case of tuberculosis should receive chemoprophylaxis for twelve months if their reaction to the Mantoux test with 5 TU of PPD is 5 mm. or more of induration. In such instances, a 5 mm. reaction is most likely the result of exposure to tuberculosis and not a cross reaction. Those household contacts who show negative Mantoux tests should be retested every three months until at least three months have elapsed since the last exposure. If the skin test converts, chemoprophylaxis should be instituted.

An alternative approach is to give chemoprophylaxis to all household contacts, including those with negative tuberculin tests. Positive reactors remain on the drug for the full course. Negative reactors should be retested three months after their last contact with the active case. If the contact has been assuredly broken and if they are still negative to tuberculin, chemoprophylaxis may be discontinued. When exposure may be continuous, it is desirable to give chemoprophylaxis to tuberculin negative contacts for as long as exposure con-

tinues. This may also be advisable in epidemics in closed groups and in situations where it is impossible to retest the negative reactors at regular intervals.

Other Positive Reactors

In addition to the positive reactors described above, chemoprophylaxis should be given to the following reactors with negative X-rays:

1. Converters: Known converters of all ages should receive chemoprophylaxis.
2. Positive reactors under age 20: Chemoprophylaxis is mandatory for positive reactors through the age of school entrance and for teenagers because the risk attending tuberculous infection is considerably higher in these age groups.

The World Food Problem

In May, 1967, the President's Science Advisory Committee published "The World Food Problem," a three-volume report on a year-long study.

Among the basic conclusions of the Committee's Lanel on the World Food Supply:

"1. The scale, severity and duration of the world food problem are so great that a massive, long-range, innovative effort unprecedented in human history will be required to master it."

"2. The solution of the problem that will exist after about 1985 *demands* that programs of population control be initiated now. For the immediate future, the food supply is critical."

Two other conclusions are related to agricultural and economic development, and economic assistance from developed nations.

The report is addressed principally to the problem of the food shortage that is expected to occur between 1967 and 1985, before programs of family planning can be expected to ameliorate the shortage by reducing world population growth. It has this to say, however, on the imperative necessity of reducing population growth:

"To avoid a continued worsening of the population-food situation during the years beyond 1985, that may even reach an economically or ecologically irreversible state of imbalance... the Panel is unanimous in supporting and urging, in the strongest terms, continuing and increasing emphasis upon research, technical assistance, and capital funding in family planning."

The interdependence of family planning programs and programs for improving nutrition were recognized by the Panel. Anomalous as it sounds, solution of the world food supply problem cannot succeed in the long run without successful family planning programs, but successful family planning progress connot be mounted unless nutrition, especially infant and child nutrition, is improved dramatically within the next two critical decades.

The anomaly hinges upon infant and child mortality, which is appallingly high in the malnourished infants of the developing nations. Malnutrition, especially deficiency in protein, by itself or in company with various diseases is one of the greatest child killers in the world. One of the apparent results of high child mortality is the desire of married couples in developing nations to produce relatively large numbers of children in order to be assured that some will live to maturity.

"If we assume," says the Panel on World Food Supply, "the necessary precon-

ditions for reducing fertility rates in the developing countries are low infant and child mortality and a public awareness that mortality is low, then we have the apparent paradox that a reduction in childhood mortality will reduce rather than raise the rate of popultaion growth."

In the meantime, "availability and efficacy of pills, intrauterine devices and other technical means for birth control are largely irrelevant until couples have secured the desired number of living children."

Clinical medicine, medical science, nutrition science and other health professions thus assume a place alongside agriculture and economics in the race to help the developing nations advance into industrialization before they collapse into regional or world famine.

Human Reproduction

Indications began to appear early this year that a "second generation" of contraceptive drugs, emphasizing long-term antifertility, are on the horizon.

Significant changes in state laws concerning therapeutic abortion also were seen during the year, and these were accompanied by indications of liberalizing attitudes toward pregnancy termination for medical reasons.

The American Medical Association House of Delegates adopted a major revision of policy on therapeutic abortion, but made it clear that the AMA still opposes induced abortion, except in certain circumstances. Prepared by the AMA Committee on Human Reproduction and approved by the Board of Trustees, the policy statement is a guide for local and state medical societies in states contemplating legislative reform.

"...Recognizing that there are many physicians who, on moral or religious grounds, oppose therapeutic abortion under any circumstances," the new policy statement says, "the American Medical Association is opposed to induced abortion except when there is documented medical evidence that":

1. Continuance of the pregnancy may threaten the health or life of the mother, or

2. The infant may be born with incapacitating physical deformity or mental deficiency, or

3. Continuance of a pregnancy, resulting from legally established statutory or forcible rape or incest may constitute a threat to the mental or physical health of the patient.

Two other physicians of recognized professional competence must examine the patient and concur in writing with the recommendation for therapeutic abortion, and the gynecologic procedure must be performed in a hospital accredited by the Joint Commission on Accreditation of Hospitals.

Two states, Colorado and North Carolina, enacted legislation similar to the AMA policy statement, while California incorporated in its laws a more liberal approach to abortion but did not include provisions authorizing abortion in case of suspected physical or mental damage to the unborn child.

Research on long-term contraceptive drugs was described at a meeting of Planned Parenthood Physicians in Atlanta, Ga. As reported in the Medical News section of the Journal of the American Medical Association, research centers upon: (1) implantable, sustained release preparations, and (2) two injectable contracentive drugs

that have proven safe and acceptable in clinical trials ranging up to three years in duration. Investigators indicated that testing of both types of drugs was continuing.

A scientific report of the World Health Organization urged intensified worldwide research to devise a test for predicting ovulation some days in advance. Lack of a simple, inexpensive—and above all, accurate—test for predicting ovulation is the major barrier to wider use of the "rhythm method," WHO said. The "rhythm method" of sexual continence during fertile periods of a woman's cycle is the only means of conception control sanctioned by the Roman Catholic Church and thus the only means that is fully acceptable to millions of couples throughout the world. The basic difficulty with current tests to identify fertile periods in the woman is that they are retrospective—that is, ovulation already has occurred when positive physiological signs appear.

Heart Disease

One of the largest epidemiological studies in history, designed to learn whether premature coronary artery disease can be prevented by diet, was recommended in June at a scientific session of the American Medical Association's 116th Annual Convention.

The proposed study would last five years, involve 40,000 to 100,000 men, and cost as much as $50 million.

The recommendation was made by principal investigators of the National Diet-Heart Study feasibility trials, a smaller study carried out over approximately two years with about 2,400 men aged 45 to 54 years to determine the feasibility of conducting the larger, five-year investigation.

In recommending the larger study to the National Heart Institute, the funding agency, the investigators said:

—"The incidence and mortality of premature coronary heart disease in the United States is extremely high. . .and constitutes one of the greatest challenges to preventive action confronting medical science and public health."

—"There is overwhelming evidence that the incidence of premature coronary heart disease is strongly associated with serum cholesterol level."

—"The serum cholesterol level can be safety lowered by modification of the usual American diet in ways that are acceptable to large numbers of people."

The feasibility study showed, the investigators said, that a large diet study can be conduced with both public volunteers and men confined in an institution. The food industry cooperated in preparing special fat-modified foods for the study.

The investigators suggested that the large, primary prevention study should concern married men, aged 40-59 or 45-59 at the outset, selected because or serum cholesterol levels of 250 mg/deciliter or greater. Men with high cholesterol levels should be used in the study, they said, because the risk of heart attack should be high enough to permit a definitive test with a manageable sample size.

A different approach to the investigation of ways to prevent heart disease—the Coronary Drug Project—got underway after several years of planning.

The Project is a national cooperative clinical trial with the objective of assessing efficacy of several lipid-lowering drugs in

long-term therapy of men with previous myocardial infarction.

Involved in the Project are 55 medical centers, the National Heart Association, and the funding agency, the National Heart Institute. Over the next two years about 8,400 men aged 30 to 64 years with histories of one or more verified infarctions are to be enrolled. Enrollment should be complete by July 4, 1969; the study is to be completed by July 1, 1974.

Like the Diet-Heart Study, the Coronary Drug Project is based on the hypothesis that long-term lowering of serum cholesterol in coronary-prone men may have a beneficial effect. Drugs to be tested in the Project have all been shown to influence serum lipid levels. The primary criterion of drug efficacy is to be the death rate from all causes in the drug-treated groups of men, compared with that in groups treated with placebo, according to Jeremiah Stamler, M.D., Project steering committee chairman.

Evidence was reported during the year that many Americans probably have had "silent" or unrecognized heart attacks which may be followed in time by one further attacks and incapacitation or death.

The fairly common occurrence of unrecognized myocardial infarction has long been suspected. Confirmation of the fact came from the study of 5,127 adults in the Framingham (Mass.) Heart Disease Epidemiology Study. The Framingham study, a long-term investigation of the public health aspect of heart disease conducted by the National Heart Institute, has been underway for 12 years with volunteers enrolled from the Framingham area.

Reporting data from 12 years' surveillance, William B. Kannell, M. D., and other investigators told the American College of Cardiology that, as of the summer of 1966, a total of 156, myocardial infarctions had been confirmed among persons who entered the study at ages 30 to 62. Of these, 115 had been recognized and 41 or about one in four were "silent."

Within five years, a third of the "silent" attacks had recurred and slightly more than half of these were fatal. The unrecognized infarctions were detected by means of biennial electrocardiograms taken of the study's participants.

The importance of medical examination to detect the "silent" infarct, and of medically-supervised prophylactic measures for the "silent" infarct victim, were stressed by the investigators.

Drug Abuse

Clinicians and research scientists in a number of disciplines were taking some close, serious looks at the much-publicized "mind expander" drug lysergic acid diethylamide (LSD), and reporting some disturbing findings.

In a study reported to the American Psychiatric Association's 123rd annual meeting, more than twice as many chromosomal abnormalities were found in blood cultures from a group of LSD users than in cultures from non-user control subjects. Chromosomes are the intra-cellular bodies upon which the heredity-bearing substance deoxyribonucleic acid (DNA) is arranged in orderly sequence.

Chromosome abnormalities are frequently associated with congenital defects in offspring. In this case, the investigators noted, "it is too early to assess the significance of the findings and the effect, if any, on future generations."

Eight LSD users, volunteers from a lo-

cal "hippie" community, were used in the study by Jose Egozcue, M. D., and Samuel Irwin, Ph. D., Oregon Regional Primate Center, Portland. Blood cultures from only two of the eight users had no significant number of chromosome breaks, and those two subjects also reported taking the smallest average doses of LSD, the investigators said. The number of LSD doses taken by the users ranged from four to 200. In blood cultures from nine control non -users, chromosome breaks were found in significant number only in material from one subject who had received a series of x-ray treatments 22 years previously. X-rays are known to produce chromosome breakage.

In material from two of the users, the chromosome abnormalities resembled the Philadelphia 1-type chromosome observed previously only in patients with chronic myelogenous leukemia.

Another finding that LSD is associated with increased chromosome breakage was reported by Maimon M. Cohen, Ph.D., and co-workers at the State University of New York at Buffalo.

Dr. Cohen sounded the first such warning about LSD in the spring when he reported observing chromosome damage, similar to that caused by radiation, in human blood preparations to which LSD was added in the test tube.

Later, chromosome breaks were observed in blood preparations from LSD users and, perhaps potentially the most serious, in blood preparations from infants that had been exposed before birth to LSD ingested by their mothers.

Artificial and Transplanted Organs

The first successful transplantation of an internal organ-a kidney-from one human being to another took place more than a dozen years ago.

Today, the transplantation of internal organs is still a highly experimental procedure on the frontier of medicine, of limited use in saving or extending lives but incredibly lucrative in insights for investigators in immunology and other fields.

In one area, kidney transplantation, the transfer of an internal organ from human to human has become a relatively reliable clinical procedure with an increasingly good record of extending life usefully.

According to the scientific journal "Transplantation," nearly 1,200 kidney transplantations have been performed worldwide, and among those patients 55 per cent survived one year or longer after the procedure if the kidney donor and recipient are related. Among cases done since January 1, 1965, the year-or-longer survival rate is 65 per cent when donor and recipient are related.

Increasing success is in large part due to better understanding of the immunological processes by which the human body rejects foreign tissue.

A battery of drugs is now available to suppress the immunological attack which the recipient's body mounts against a transplanted organ.

A non-pharmacologic approach to immunosuppression, the use of anti-lymphocyte serum (ALS) recently has become increasingly successful in transplant surgery. Anti-lymphocyte serum is obtained from animals immunized against human lymphocytes. Injected into the potential recipient of a transplanted organ, the anti-lymphocyte antibodies contained in ALS selectively suppress the immune reaction.

The entire serum is no longer necessary, however. Most surgical teams use anti-lym-

phocyte globulin (ALG), an extract of the antilymphocyte antibodies.

A combination of ALG and immunosuppressive drug therapy was used by University of Colorado surgical teams in achieving longsurviving liver transplants in four patients.

By mid-November three of the patients, all young girls, had survived longer than any other liver transplant recipients in the short history of liver transplant surgery. The dates of the operations were July 23, August 1, September 5 and October 8. The longest previous survival was about a month, in a woman also at the University of Colorado Medical Center.

A spokesman for the University of Colorado teams said that the critical factors in achieving long-term survival were the use of ALG in immunosuppression, and improved procedures for preserving the donor organ. Livers are obtained from cadavers and are transplanted within six to eight hours after the donor's death. By using a preservation method that combines hypothermia and hybaroxia (high-pressure oxygen atmosphere), the Colorado group has been able to delay damaging tissue changes in the isolated liver. Improved organ preservation also permits the surgeons to adopt a less hurried approach to the transplantation procedure.

A team of Milwaukee surgeons successfully used cadaver livers outside the body to support patients whose own livers had temporarily lost function.

Four patients in hepatic coma were treated by perfusing their blood through cadaver livers, reported Joseph C. Darin, M. D., and associates, Marquette University School of Medicine. Three of the patients regained consciousness after perfusion and seemed to be regaining liver function when they died of causes unrelated to liver disease. The fourth patient was moribund when perfusion was started and the procedure appeared to have no effect, the investigators reported.

The Multiple Roads of Cancer Research

An experimental method of treating cancer by selectively starving tumor cells of essential amino acids has prolonged the lives of a number of patients, two University of Chicago cancer researchers reported.

Albert B. Lorincz, M. D., and Robert E. Kuttner, Ph. D., described their studies at the 116th Annual Convention of the American Medical Association.

Biochemical assays of tumor cells have shown that every tumor has individual and distinctive amino acid requirements, Drs. Lorincz and Kuttner said.

Clinical experience with carefully selected, volunteer patients has indicated that, when the amino acid content of a tumor is determined through assay, it can sometimes be caused to regress when the patient is fed a diet that is deficient in the specific amino acids that the tumor requires. Of 30 patients so treated, the investigators said, 20 had experienced comfortable prolongation of life from four to 22 months. Patients were not selected for the experimental diet-therapy program unless usual clinical procedures had been proven inapplicable.

Vaccines: A Success Story

Basic research which seeks the cause of cancer may get a boost from the work of another team of investigators, who worked out the intricate molecular structure of the enzyme ribonuclease.

David Harker, Ph. D., who has been studying the enzyme's protein structure for 16 years, commented in announcing the results of the investigation:

"The life process depends upon the orderly behavior of complex forces acting within protein molecules, and their interactions and reactions with neighboring molecules.

"It is possible that, when the atomic structures of proteints are altered in some manner, there may be a relationship to cancer."

Ribonuclease is a protein, as are most enzymes.

Dr. Harker is director of the Center for Crystallagraphic Research at Roswell Park Memorial Institute, Buffalo, N. Y., where he and co-workers conducted the ribonuclease research. More than a half-million reflections were taken of ribonuclease crystals in the investigators' x-ray diffraction unit in order to precisely map the position of the 1,000-plus atoms in the ribonuclease molecule.

Ribonuclease works within the cell to break down ribonucleic acid, and thus exert a control on cell growth; at the cell's death, the enzyme acts as a "housecleaner" to remove freed ribonucleic acid.

Basic research in virology and immunology is paying off handsomely for medicine through enhanced ability to produce effective vaccines.

Measles (rubeola) vaccine has proven so effective that some clinicians speak of using it to "eliminate" the disease from the United States. An anti-measles vaccination campaign is being conducted by the American Medical Association and U. S. Public Health Service, and its success can be measured by the fact that fewer measles cases were reported during the first half of 1967 than in any comparable period since measles record-keeping began in 1912. Live-virus measles vaccine is recommended by many authorities now, in preference to killed-virus types.

At least four new vaccines should reach important stages of development within the next few months.

Licensure of a mumps vaccine was expected before the end of the year, according to one of its developers, Maurice R. Hilleman, Ph. D., Merck Institute for Therapeutic Research. It has been given to approximately 6,500 persons in experimental clinical trials "with excellent serologic response and protective efficacy, and without untoward clinical effect," Dr. Hileman reported.

A vaccine against German measles (rubella) may be generally available within two years, according to investigators at the National Institutes of Health. Clinical trials with an experimental vaccine have been underway more than two years, with more than 500 persons vaccinated.

University of Chicago investigators hope during the next year to immunize about 200 children with an experimental vaccine designed to prevent streptococcal infections of the type which often are responsible for rheumatic fever and glomerulonephritis. About 40 adults and 25 infants have received the vaccine since its development last year. Twenty of the 25 infants responded with production of antibodies capable of destroying streptococcus, reported Eugene N. Fox, Ph. D., Albert Dorfman, M. D., and associates.

A vaccine to prevent erythroblastosis fetalis (Rh disease) also may be licensed in 1968. The vaccine is an anti-Rh immune

globulin which is given to an Rh-negative mother after the birth of her first Rh-positive infant. The globulin acts to prevent an immunological attack by the mother's body upon the fetus during a second pregnancy, presumably through a mechanism of antibody-induced immunosuppression.

Interferon: A New Lance for the Armory?

Parallel with advances in vaccine development came indications that the antiviral agent interferon may yet become a weapon in the armory of clinical medicine.

Interferon, discovered by English investigators in 1956, is a protein produced by cells in response to virus infection and to some non-viral substances which are capable of entering the cell. It appears to act upon other cells to stimulate production of a protein which inhibits virus replication.

Ever since the discovery of interferon medical scientists have been fascinated with the idea that a wide variety of viral diseases could be prevented if interferon production could be stimulated to high levels within the human body. Efforts to "harvest" interferon from animals for use in human beings proved of no value: interferon is species specific, meaning that interferon from one species does not stimulate anti-viral activity in any other species.

Among substances being investigated as a harmless means of stimulating interferon production are: (1) a double strand of ribonucleic acid (RNA) stripped from certain viruses, which appears to jog cells into interferon production without causing disease, and (2) an industrially-synthesized giant molecule called pyran.

Although interferon produced within the body is much more potent than that passively injected, medical scientists are continuing efforts to obtain satisfactory interferon production in cultures of human cells.

NOTICIAS

Locales

REUNIONES

Abril 16 — Asamblea Anual de la Asociación de Enfermería Comprensiva.

Abril 17-18 — Conf. de Pediatría auspiciada por la Academia Americana de Práctica General.

Abril 20 — (tentativo) — Primera reunión ordinaria de la Cámara de Delegados de la Asociación Médica de Puerto Rico.

DUPLICADORA

Deseamos informar a todos los miembros de la Asociación que ésta acaba de adquirir una duplicadora para la preparación de programas, tarjetas, reimpresos, recetarios, etc.

La adquisición de este equipo constituye un gran paso de avance, por cuanto permite una mejor y más rápida impresión de los trabajos a realizarse y deberá redundar en economía para la Asociación.

SECCION DE OFTALMOLOGIA Y OTORRINOLARINGOLOGIA

En la última reunión anual de la Sección de Oftalmología y Otolaringología se nombró la Junta Directiva para el año 1967-1968.

La Junta Directiva quedó compuesta por los siguientes miembros:

Kernell Ocasio Cabañas, M.D., Presidente
Nelson Fernández Blasini, M.D., Presidente-Electo y Tesorero,
Antonio Rullán, M.D., Secretario por Otolaringología
Walter Kleis, M.D., Secretario por Oftalmología.

Noticias

NEW BOOKS

List of books recently acquired by the Library of the University of Puerto Rico, Medical Sciences Campus.

Biology. Anatomy. Physiology

1. Ciba Foundation Study Group no. 23, London, 1965. Egg implantation. Boston, Little, Brown, 1966.

2. Ganong, William F. Review of medical physiology. 3d ed. Los Altos, Calif., Lange Medical Publications, 1967.

3. Gardner, Ernest. Anatomy, a regional study of human structure. 2d ed. Philadelphia, Saunders, 1963.

4. Heinmets, Ferdinand. Analysis of normal and abnormal cell growth. New York, Plenum Press, 1966.

5. Jonas, Hans. The phenomenon of life: toward a philosophical biology. 1st ed. New York, Harper and Row, 1966.

6. Mercer, Edgar H. Electron microscopy. 2d ed. Oxford Blackwell Scientific Publications, 1966.

7. Watson, J.D. Molecular biology of the gene. New York, W. A. Benjamin, 1965.

8. Weidenreich, Franz. Apes, giants and men. Chicago, University of Chicago Press, 1946.

Biochemistry

1. Beaton, George H.Nutrition: a comprehensive treatise. v.3. Nutritional status: Assessment and application. New York, Academic Press, 1966.

2. Braverman, Joseph B.S. Introduction to the biochemistry of foods. Amsterdam, New York, Elsevier Pub. Co., 1963.

3. Henley, Keith S. Enzymes in serum; their use in diagnosis. Springfield, Ill., C.C. Thomas, 1966.

4. International Symposium on the Biochemistry of the Retina. 1st, London, 1964. Biochemistry of the retina. London, New York, Academic Press, 1965.

5. Kleiner, Israel Simon. Laboratory instructions in biochemistry. 7th ed. Saint Louis, Mosby, 1966.

6. Robinson, Frank Arnold. The vitamin cofactors of enzyme systems. 1st ed. Oxford, New

York, Pergamon Press, 1966.

7. Van Peenen, Hubert J. Biochemical genetics. Springfield, Ill., C.C. Thomas, 1966.

8. Wolf, Arnold Veryl. Aqueous solutions and body fluids. New York, Hoeber Medical Division, 1966.

Pharmacology

1. Cutting, Windsor Cooper. Handbook of pharmacology. 3d ed. New York, Appleton-Century-Crofts, 1967.

2. Evans, Ronald Major. The chemistry of the antibiotics used in medicine. 1st ed. Oxford, N.Y., Pergamon Press, 1965.

3. Goldzieher, Joseph William. Oral contraception: mechanism and management. Springfield, Ill., C.C. Thomas, 1966.

4. Grosourdy, Renato de. El médico botánico criollo. París, Librería de Francisco Brachet, 1864.

5. U.S. Public Health Service. The health consequences of smoking. Washington, D. C., 1967.

Parasitology. Bacteriology

1. Cox, Kaye B. The effects of Forssman antigen on adult *Schistosoma mansoni in mice*. Dissertation submitted in partial fulfillment of the requirements of the Doctor of Philosophy degree. San Juan, Puerto Rico, Department of Medical Zoology, School of Medicine, University of Puerto Rico, 1967.

2. Foster, William Derek. A history of parasitology. Edinburgh, E. & S. Livingstone, 1965.

3. Londoño, Iván. Especificidad de anticuerpos en la trichinosis experimental de la rata y su localización en las globulinas del suero. Disertación sometida como uno de los requisitos necesarios para la obtención del grado de Master en Ciencias en el Departamento de Biología de la Universidad de Puerto Rico. Recinto de Río Piedras, San Juan,P.R., Universidad de Puerto Rico, 1967.

4. Stephenson, Marjory. Bacterial metabolism. Cambridge, Mass. M.I.T. Press, 1949.

Pathology

1. Alejandrino, Adoración L. A biochemical approach to the problem of neoplastic metastasis. Dissertation submitted in partial fulfillment of the requirements of Master of Science. San Juan, Puerto Rico, Department of Biochemistry and Nutrition, School of Medicine, University of Puerto Rico, 1967.

2. Association of Vitamin Chemists. Methods of vitamin assay. 3d ed. New York, Interscience Publishers, 1966.

3. Boyd, William. Pathology for the physician. 7th ed., thoroughly rev. Philadelphia, Lea and Febiger, 1965.

4. Daudel, Pascaline. Chemical carcinogenesis and molecular biology. New York, Interscience Publishers, 1966.

5. Evans, R. W. Histological appearances of tumours. 2d. ed. Baltimore, Williams and Wilkins, 1966.

6. Hoffman, Frederick L. Cancer in México. Rochester, N.Y., American Association for Cancer Research, 1967.

7. Larionov, Leonid Fedorovich. Cancer chemotherapy. 1st. ed. Oxford, New York, Pergamon Press, 1965.

8. Morgan, Rose M. Guide questions for medical technology examinations. Springfield, Ill., C. C. Thomas, 1966.

9. Reid, Eric. Biochemical approaches to cancer. 1st ed. Oxford, New York, Pergamon Press, 1965.

10. Sunderman, Frederick William. Clinical pathology of the serum electrolytes. Springfield, Ill., C.C. Thomas, 1966.

Hematology

1. Marcus, Aaron Jacob. The physiology of blood platelets. New York, Grune and Stratton, 1965.

2. Salzman, Edwin W. Hemorrhage and thrombosis, a practical clinical guide. Boston, Little, Brown and Co., 1965.

3. Seegers, Walter Henry. Blood clotting enzymology. New York, Academic Press, 1967.

4. Szirmai, E. Nuclear hematology. New York, Academic Press, 1965.

FUNERAL COSTS AND DEATH BENEFITS

The "high cost of dying" has become of increasing concern to many people — bereaved families, ministers, labor welfare directors, doctors. Some have found a way to arrange for appropriate, dignified funerals at a moderate cost.

How this can be done is outlined in FUNERAL COSTS AND DEATH BENEFITS, a new Public Affairs Pamphlet by Sidney Margolius, a leading expert on consumer problems. In this pamphlet

Margolius discusses the pricing system for funerals, suggests how to keep costs modest, and summarizes the financial benefits that may be available to meet the expenses. FUNERAL COSTS AND DEATH BENEFITS is available for 25 cents from the Public Affairs Committee, 381 Park Avenue South, New York, N.Y. 10016.

Criticism of high costs, Margolius points out, does not necessarily mean that funeral directors are making excessive profits. It is, in many instances, criticism of needlessly elaborate services and materials. Further, labor unions and welfare organizations are disturbed to find that "funeral costs have marched upward in close relationship to death benefits provided by employers and unions" — often leaving little if anything for remaining medical bills and other emergency expenses faced by the family.

One basic fact that may be unfamiliar to many people is that "the price of the entire funeral varies with the type of casket chosen, and a more expensive casket may lead to a disproportionate increase in the cost of many other items furnished." And even for those who may prefer the costlier arrangements, there are ways of keeping costs down. Margolius outlines four basic types of group efforts in that direction:

1. *Arrangements by the group itself.* A New York union, for example, has arrangements with several funeral establishments. A burial — simple but dignified — can cost as little as $315. Even for families that prefer a costlier casket, these group arrangements provide a saving of 33⅓ per cent. "A funeral that normally costs $600, costs the family using this...plan $400." Thus, the bereaved family will still have available for its other needs much of the death benefits, which, in this union, is a minimum of $1,000, and $2,000 or more for those in the union welfare plan at least five years.
2. *Checkup or supervisory activities.* Other unions may have a committee "to check on prices charged members' families by morticians...This method may not result in as low costs as (the plan described above), but it is simpler for a small group to operate."
3. *Joining with others in a burial co-op.* Margolius found that such groups "avoid any pressure on the family to buy additional services or goods which can raise the cost of a funeral as much as $200. Thus, the average cost reported by some co-op establisments typically is one-third less than the amount of the national average."
4. *Memorial associations.* These associations — usually initiated by church groups, co-ops, unions, or other community groups — "seek both to control funeral costs and to ease the worries of older people over what plans they ought to make, and simplify arrangements for grief-stricken families." They stress "pre-planning." There are an increasing number of memorial associations, and they usually include people of several different faiths. "The effectiveness of these associations is demonstrated by the record of the Chicago Memorial Association... Its members have been able to reduce the costs to about one-fourth of the average for the area. This society...also has credit union arrangements so members can open accounts to insure payment of burial or cremation charges."

But even with individual, rather than group, arrangements, advance planning can help ease the strain and the expense of a funeral. Margolius points out that "it is helpful to have an understanding with your family about the arrangements you wish," and offers specific suggestions and cautions.

The final pages of FUNERAL COSTS AND DEATH BENEFITS offer guidance on veterans' benefits, Social Security, and other benefits for which the survivors may be eligible. "A will and funeral instructions are essential to save your family expense and time in settling your estate, to make sure your property is distributed as you want," and to make known your wishes in regard to services, interment, cremation, etc. Also, Margolius stresses, keep "tideover" money — at least four weeks' living expenses — available, or know a source from which it can be borrowed until insurance and Social Security checks arrive.

In summary, Margolius shows that there is more freedom of choice of funeral services and goods (and, consequently, costs) than many people realize. His pamphlet is a simple, helpful guide to a difficult problem all families have to face.

FUNERAL COSTS AND DEATH BENEFITS is available for 25 cents from the Public Affairs Committee, a nonprofit educational organization, 381 Park Avenue South, New York, N.Y. 10016.

Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Mar. 28-30 — *Current Concepts in Physiology of Respiration, Circulation and Electrolyte Metabolism.* Co-sponsored with the American Physiological Society, to be held at The Somerset Hotel, Boston, Mass.

Apr. 22-26 — *Clinical Endocrinology — Recent Advances in Diagnosis* and Treatment. Mayo Graduate School of Medicine (University of Minnesota) and Mayo Clinic, Rochester, Minn.

May 12-15 — *Frontiers in Gastroenterology.* University of Pennsylvania School of Medicine, to be held at the Bellevue Stratford Hotel, Philadelphia, Pa.

May 20-24 — *The Prevention and Early Detection of Disease in Clinical Practice.* University of Pennsylvania School of Medicine, Philadelphia, Pa.

May 27-29 — *Auscultation of the Heart.* Hahnemann Medical College and Hospital, to be held at The Sheraton Hotel, Philadelphia, Pa.

June 3-7 — *Intensive Care Units.* University of Cincinnati Medical Center and V.A. Hospital, Cincinnati, Ohio.

June 10-14 — *Basic Principles in Internal Medicine* — 1968. University of Iowa School of Medicine, Iowa City, Iowa.

June 17-19 — *Intensive Care Units.* University of Colorado Medical Center, Denver, Colo.

June 19-21 — *Infectious Disease: Mechanisms and Manifestations.* University of Maryland School of Medicine, Baltimore, Md.

OTHER MEETINGS

Apr 11-13 — *Symposium on Correlations in Medicine: The Clinician and the Laboratory.* Mound Park Hospital Foundation, Department of Medical Education of the Mound Park Hospital, Bay Pines V.A. Hospital, Pinellas County Medical Society, Florida Academy of General Practice.

Mar. 30-31 — Second National Congress on Medical Ethics, Chicago, Ill., Drake Hotel.

Apr. 4-6 — Board of Trustees, Chicago, Ill., AMA Headquarters.

Apr. 4-6 — Third National Conference on Health Education of the Public, DHE, Chicago, Ill., Pick-Congress Hotel.

Apr. 11 — AMA Interspecialty Committee, Chicago, Ill., AMA Headquarters, Board Conference Room, 9:00 a.m. - 5:00 p.m.

Apr. 19 — Residency Review Committee for Colon and Rectal Surgery, Philadelphia, Pa., Barclay Hotel, 1:30 p.m.

**Apr. 22* — Committee on Occupational Toxicology, San Francisco, Calif., Hilton Hotel, 12:00 noon — 5:30 p.m.

**Apr. 22* — Residency Review Committee for Thoracic Surgery, Pittsburgh, Pa., Hilton Hotel, 5:00 p.m.

Apr. 27 — Residence Review Committee for Psychiatry and Neurology, DGME, Chicago, Ill., Pick-Congress Hotel, 9:00 a.m.

Apr. 28 — Council on Environmental and Public Health, Chicago, Ill., Drake Hotel, all day.

Apr. 29-30 — Fifth Congress on Environmental Health Problems, Chicago, Ill., Drake Hotel, all day.

May 6-7 — Residency Review Committee for Urology, DGME, Ponte Vedra, Fla., Ponte Vedra Club, 9:00 a.m.

May 10-11 — Council on Mental Health, Chicago, Ill., Drake Hotel.

May 10-12 Council on Occupational Health, Fort Lauderdale, Fla., Pier 66, 9:00 a.m. - 5:00 p.m.

**May 10-11* — Residency Review Committee for Pediatrics, DGME, Chicago, Ill., Drake Hotel, 9:00 a.m.

May 16-18 — Board of Trustees, Chicago, Ill., AMA Headquarters.

**May 20*-BV — Residency Review Committee in Internal Medicine, DGME, Chicago, Ill., Drake Hotel, 9:00 a.m.

May 25-26 — Residency Review Committee for Obstetrics-Gynecology, Hot Springs, Va., Homestead Hotel, 2:30 p.m.

June 12-15 — Board of Trustees, San Francisco, Calif.

June 14-16 — Council on Medical Education, San Francisco, Calif.

July 11 — AMA Interspecialty Committee, Chicago, Ill., AMA Headquarters, Board Conference Room, 9:00 a.m.-5:00 p.m.

July 21 — Council on Environmental and Public Health, Denver, Colo, Denver-Hilton Hotel, all day.

MANUSCRIPT AWARD FOR 1968 BY THE OBSTETRICS AND GYNECOLOGY SPECIALTY GROUP OF THE UNITED STATES SECTION INTERNATIONAL COLLEGE OF SURGEONS

The Obstetrics and Gynecology Specialty Group of the United States Section of the International College of Surgeons is pleased to announce a competition for an award to be given the author of a manuscript selected by the Prize Committee of the Group. This award will consist of an invitation to present the winning paper at our meetings in Honolulu, Hawaii and Tokyo, Japan, including a round-trip ticket, hotel expenses and $10.00 per diem.

The rules of the competition are as follows:

- Fellows of the International College of Surgeons are not eligible. Contestants must be (a) interns, residents or graduate students in the field of obstetrics and/or gynecology. Contestants must hold the degree of Doctor of Medicine from an accredited college of medicine, and must be residents of the United States.
- Manuscripts are to represent only original work by the author without co-authorship. Manuscripts are not to exceed 5,000 words. They should be typewritten on one side of each sheet only, double-spaced and with generous margins. Ilustrations, if indicated, should accompany the manuscript. Original drawings or glossy photographic prints should be numbered on the back and legends for the ilustrations should be provided. A mark of identification, or the author's nom de plume, should be penciled on the back of each ilustration. Tables should be numbered and submitted on separate sheets. References should be listed at the end of the article and numbered, naming the author of the reference, the pages on which the article was printed and the year of publication.
- To conceal the identity of the author, manuscripts must be *submitted under an assumed name*. The manuscript must be accompanied by a sealed envelope, containing a card bearing the assumed name of the author, the title of the manuscript and the true name of the author, his degrees, titles and address. An original and three copies of each manscript (carbon, photostatic, memeographic or other) and illustrations must be submitted on or before April 15, 1968 to Doctor Harvey A. Gollin, Chairman of the Prize Committee, 55 East Washington Street, Chicago, Illinois 60602.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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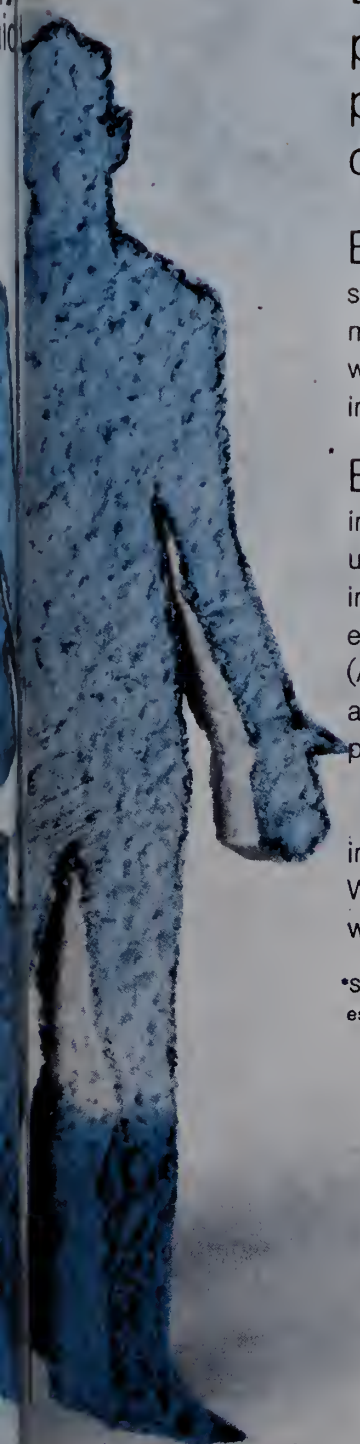
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Because Lasix starts to relieve edema promptly...helps you to maintain patients edema-free with more precise control than with thiazides.

Because Lasix's action is prompt and of comparatively short duration, you can evaluate patient response and make any necessary dosage adjustments more quickly than with longer-acting diuretics. You also spare patients the inconvenience of prolonged diuresis.

Because of its wide range of efficacy, Lasix can be used in all degrees of cardiac edema. Mild cardiac edema can usually be relieved with low, once-daily doses of Lasix—or an intermittent dosage schedule may be used. In more severe edemas, higher doses provide appropriate response. (A maximum daily dose of 200 mg. should not be exceeded; and it should be kept in mind that, as with thiazides, some patients may experience profuse diuresis at lower doses.)

These advantages of Lasix have been demonstrated in clinical practice in almost all countries in the Western World.* In England, and in many other countries, it is the most widely prescribed diuretic.

*Since introduction in this country prescription surveys indicate that an estimate of over 500,000 patients have been treated with Lasix.

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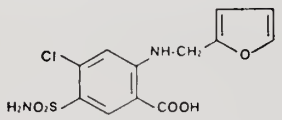
For most patients with cardiac edema... the response you want by selecting the dosage they need.

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WARNING—Lasix (furosemide) is a new, potent diuretic, which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Lasix (furosemide) is a new diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by: a high degree of efficacy; a rapid onset of action; a comparatively short duration of action; a ratio of minimum to maximum effective dose higher than 1:10; the fact that it acts not only at the proximal and distal tubule but also at the ascending limb of Henle's loop.

Chemistry—Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The structural formula is as follows:



Indications—Lasix (furosemide) is indicated for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix (furosemide) is particularly useful when an agent with greater diuretic potential than those commonly employed is desired. Until further clinical experience is accumulated, Lasix (furosemide) is not recommended for use in hypertension.

Contraindications—Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound. Until further experience in children is accumulated, therapy with Lasix (furosemide) should be avoided.

Supplementary Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids. Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter and abnormalities corrected or the drug temporarily withdrawn. **In patients with hepatic cirrhosis and ascites Initiation of therapy with Lasix (furosemide) is best carried out in the hospital.** Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. As with any new drug, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical. There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred. Based on a large survey of physicians and hospitals, both American and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.

Usage in Pregnancy—The use of any drug in pregnancy, lactation or in the childbearing age group requires that the potential benefits of the drug be weighed against possible hazards to the mother and child. Reproduction studies with Lasix (furosemide) in mice, rabbits, and rats have produced no evidence of drug-induced fetal abnormalities. However, Lasix (furosemide) has had only limited use in pregnant patients.

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix (furosemide) is administered, since Lasix (furosemide) potentiates the hypotensive effect of antihypertensive medications. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration which should be avoided, particularly in patients with renal insufficiency. Although no pronounced effect on carbohydrate metabolism has been demonstrated, periodic checks on urine and blood glucose should be made in diabetic patients receiving Lasix (furosemide). Occasional increases in blood glucose have occurred during therapy with Lasix (furosemide). Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Infrequent skin rash, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur. A single case of thrombocytopenia has been reported in which Lasix (furosemide) was considered to be the causative agent. There have been a few instances of leukopenia and one report of acute pancreatitis although relationship to the drug has not been established. Lasix (furosemide) induced diuresis has occasionally been accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, and urinary frequency.

Dosage and Administration—The usual dose of Lasix (furosemide) is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). Based on completed studies, a maximum daily dose of 200 mg. should not be exceeded. Higher doses are currently under investigation. The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

How Supplied—Lasix (furosemide) is supplied as white, monogrammed, scored tablets of 40 mg. in amber bottles of 100.

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When oppressive feelings and psychic tensions are severe and cooperation with the physician poor, it may be helpful to add adjunctive Valium (diazepam), 10 mg or 5 mg t.i.d., to the coronary patient's regimen. Valium (diazepam) helps to promote the needed relaxation that the patient requires to make him less preoccupied with his condition and more inclined to cooperate in, and benefit from, the total therapeutic program. Valium (diazepam) may be administered in the presence of secondary depressive symptoms.

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(5 mg or 10 mg t.i.d.)

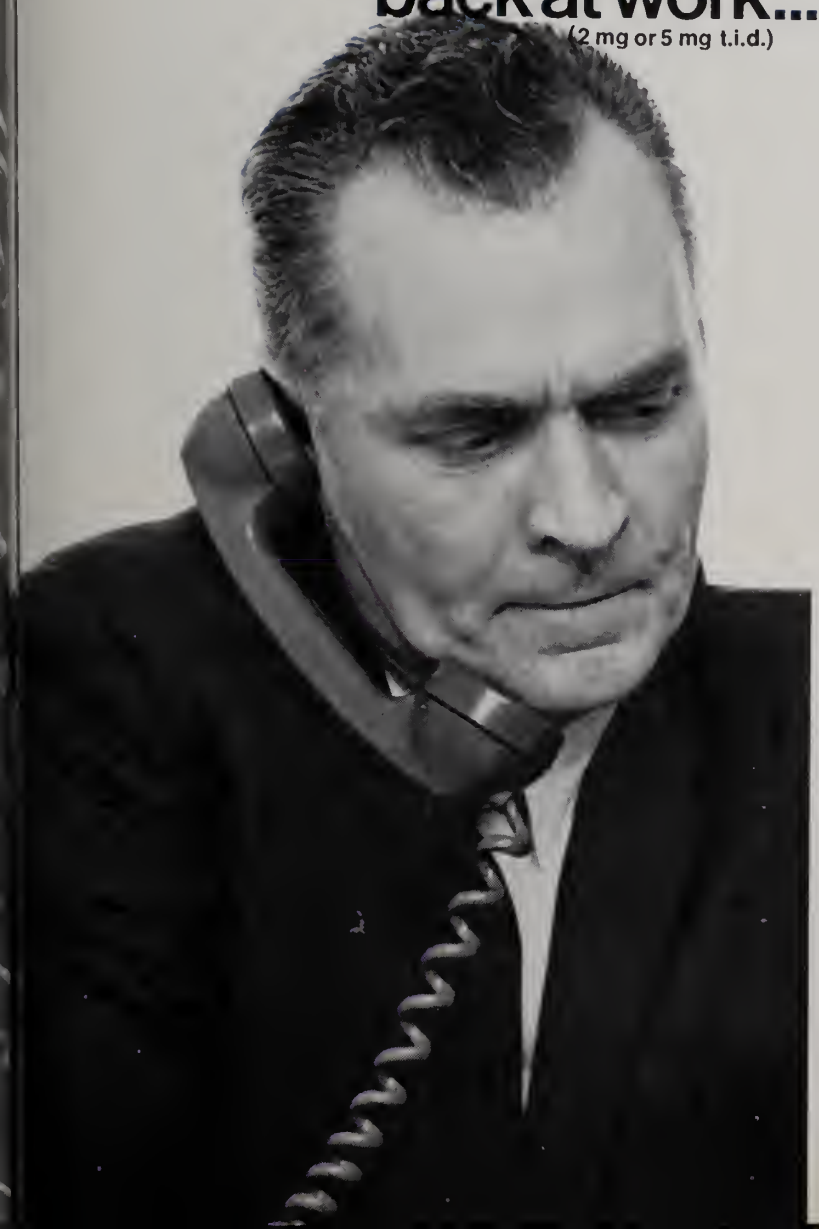


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(2 mg or 5 mg t.i.d.)

The heart patient who leaves the hospital to enter a period of slow restorative treatment is often forced to make emotionally difficult adjustments. The resulting stress of this period may again cause psychic tension to mount to potentially harmful levels. To augment your reassurance and the emotional support of his family, a 2 mg or 5 mg t.i.d. regimen of Valium (diazepam) can reduce psychic tension and thereby help the patient to accept necessary restrictions more calmly, and to adjust to his illness more realistically.

Getting back to work presents additional stresses for the cardiac patient. There are often anxiety-producing features in the job which can be more significant than the physical or intellectual demands of the work. Valium (diazepam), 2 mg or 5 mg t.i.d., may be a useful adjunct to reduce overreaction to these stresses and thus help the patient to face job situations more calmly and rationally.

back at work...
(2 mg or 5 mg t.i.d.)



Valium® (diazepam)
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and for the patient with tension-induced sleeplessness, remember the value of an extra tablet at bedtime

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states, moderate to severe psychoneurotic states with anxiety, apprehension or agitation alone or with depressive symptoms; somatic complaints which are concomitants of emotional factors; acute agitation due to alcohol withdrawal; muscle spasm associated with cerebral palsy and athetosis.

Contraindications: Infants, patients with history of convulsive disorders, glaucoma or known hypersensitivity to drug.

Warning: Not of value in the treatment of psychotic patients, and should not be employed in lieu of appropriate treatment.

Precautions: Limit dosage to smallest effective amount in elderly or debilitated patients (not more than 1 mg, one or two times daily initially) to preclude ataxia or oversedation, increasing gradually as needed or tolerated. As is true of all CNS-acting drugs, until correct maintenance dosage is established, advise patients against possibly hazardous procedures requiring complete mental alertness or physical coordination. Driving during therapy not recommended. In general, concurrent use with other psychotropic agents is not recommended. If such combination therapy is used, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, barbiturates, MAO inhibitors and other antidepressants. Advise patients against simultaneous ingestion of alcohol or other CNS depressants. Safe use in pregnancy not established. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Periodic blood counts and liver function tests advisable in long-term use. Cease therapy gradually.

Side Effects: Side effects (usually dose-related) are fatigue, drowsiness and ataxia. Also reported: mild nausea, dizziness, blurred vision, diplopia, headache, incontinence, slurred speech, tremor and skin rash; paradoxical reactions (excitement, depression, stimulation, sleep disturbances, acute hyperexcited states, hallucinations); changes in EEG patterns during and after drug treatment. Abrupt cessation after prolonged overdosage may produce withdrawal symptoms (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating) similar to those seen with barbiturates, meprobamate and chlordiazepoxide HCl.

Dosage—Adults: Mild to moderate psychoneurotic reactions, 2 to 5 mg b.i.d. or t.i.d.; severe psychoneurotic reactions, 5 to 10 mg t.i.d. or q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; muscle spasm with cerebral palsy or athetosis, 2 to 10 mg t.i.d. or q.i.d.

Geriatric patients: 1 or 2 mg/day initially, increase gradually as needed and tolerated. (See Precautions.)

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50 and 500.

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Administration and Dosage: Apply sparingly to the affected area 3 or 4 times daily.

Contraindications: Tuberculosis of the skin, herpes simplex, chicken pox and vaccinia.

Precautions and Side Effects: Do not use in the eyes or in the ear (if drum is perforated). A few individuals react unfavorably under certain conditions. If side effects are encountered, the drug should be discontinued and appropriate measures taken. Use on infected areas should be attended with caution and observation, bearing in mind the potential spread of infection and the advisability of discontinuing therapy and/or initiating antibacterial measures. Generalized dermatological conditions may require systemic corticosteroid therapy. Steroid therapy, although responsible for remissions of dermatoses, especially those of allergic origin, cannot be expected to prevent recurrence. The use over extensive body areas, with or without occlusive nonpermeable dressings, may result in systemic absorption. Appropriate precautions should be taken. When occlusive nonpermeable dressings are used, miliaria, folliculitis, and pyodermas will sometimes develop. Localized atrophy and striae have been reported with the use of steroids by the occlusive technique. When occlusive nonpermeable dressings are used, the physician should be aware of the hazards of suffocation and flammability. The safety of use on pregnant patients has not been firmly established. Thus do not use in large amounts or for long periods of time on pregnant patients.

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This one did: A 42-year-old fireman fell and suffered a fracture of his left wrist. When pressure and edema appeared to be increasing under the cast, Ananase was used adjunctively for a trial period of 24 hours. "When seen the next morning, all edema and pressure had disappeared." Marked relief was experienced with no further treatment.[1]

When the effect of Ananase on inflammation and edema was compared with the expected response to conventional therapy, without Ananase, "superior" results were obtained with Ananase in 83% of 18 fracture cases observed.[1]

Your own experience will confirm the efficacy of Ananase in helping to reduce inflammation and edema and speeding the healing process. For best results give Ananase early and in maximum dosage.

Usual Adult Dose: Initially, two tablets four times daily. For maintenance, one tablet three or four times daily.

Side Effects: Ananase has a wide margin of safety. There have been few toxic effects reported. It should be used with caution in patients with abnormalities of the blood clotting mechanism, such as hemophilia, or with severe hepatic or renal disease.

Supplied: Bottles of 100 and 500 tablets, each tablet containing 50,000 Rorer units.

One Rorer unit of protease activity is defined as that amount of enzyme which will so hydrolyze a standardized casein substrate at pH 7.0 and 25° C temperature as to cause a change in absorbance of 1 x 10^{-5} at 280 mu per minute of reaction time.

1. Cirelli, M. G.: Delaware M. J. *34*:159 (June) 1962.

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When your patients expect a lot...

like relief from hypertensive symptoms
(headache, fatigue, nervousness, palpitation or insomnia, for example)

like an up-to-date, once-a-day dosage schedule
(a schedule not unlike timed-release medication, for example)

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...give them a little
(one tablet daily)

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chlorthalidone 50 mg., reserpine 0.25 mg.

Indications: Hypertension. **Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. **Warning:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Regroton should be used in pregnant patients or in women of childbearing potential only when, in the judgment of a physician, its use is deemed essential to the welfare of the patients; adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Regroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue Regroton therapy two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, Regroton should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. **Adverse Reactions:** The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. **Average Dosage:** One tablet daily with breakfast. **Availability:** Pink, single-scored tablets in bottles of 100 and 1000. (B) 46-600-B
For details, see complete Prescribing Information.

Geigy Pharmaceuticals, Division of
Geigy Chemical Corporation, Ardsley, N.Y.

Geigy

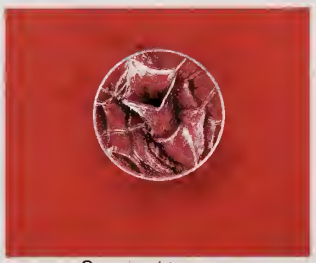

in moderate hypertension and
poorly controlled mild hypertension
(when diuretics or sedatives are inadequate, for example)

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what does CHYMORAL's faster action mean? It can mean:

- Edema and inflammation subside twice as fast—healing time cut in half.
- The patient is restored to normal activities twice as fast.
- Lesions heal in less time—and the physical appearance of the patient improves twice as fast.
- Hospital stay... convalescent period... medication costs may be cut in half.

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4123 cases **91%** had good/excellent results

3470 cases **89%** had good/excellent results



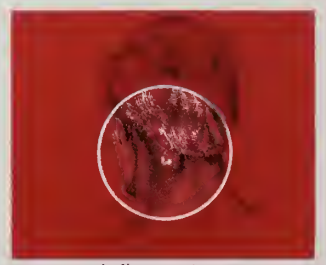
Episiotomy and pelvic inflammation



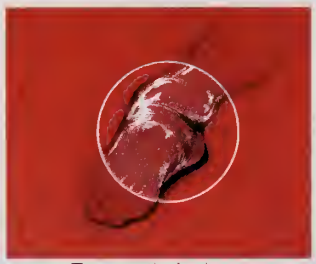
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Inflammatory dermatoses



Traumatic lesions

6929 cases **93%** had good/excellent results

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Eye, ear, nose and throat inflammations

Rx. **CHYMORAL®—Enzyme tablets**

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[1]Based on clinical reports compiled by the Medical Division of Armour Pharmaceutical Company

Otro nuevo descubrimiento de Lakeside



cuando la depresión abruma

NORPRAMIN
(clorhidrato de desipramina)

el ANTIDEPRESIVO
no-sedante de acción rápida

vence el abatimiento, levanta el ánimo, restablece la confianza

La depresión frecuentemente se caracteriza por sentimientos de culpabilidad, inutilidad, desolación y privación. Estas manifestaciones, acompañadas de síntomas tales como insomnio, malestar, tristeza y recelo, responden rápidamente al NORPRAMIN (clorhidrato de desipramina). La mejoría generalmente se manifiesta 2 a 5 días después de iniciado el tratamiento; algunas veces antes. Los pacientes con sensibilidad comprobada a estimulantes del sistema nervioso central, pueden experimentar excitación al desaparecer su depresión; en estos casos se sugiere reducir la dosis o administrar simultáneamente tranquilizantes.

Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardiacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extrapiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

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(chlordiazepoxide HCl)



For years, physicians have valued Librium (chlordiazepoxide HCl) Capsules for their reliable calming effect.



(in capsules)



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(in Libritabs™)
(chlordiazepoxide)

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver-function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 50. Libritabs™ (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

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SAN JUAN, PUERTO RICO

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SHELVES



BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

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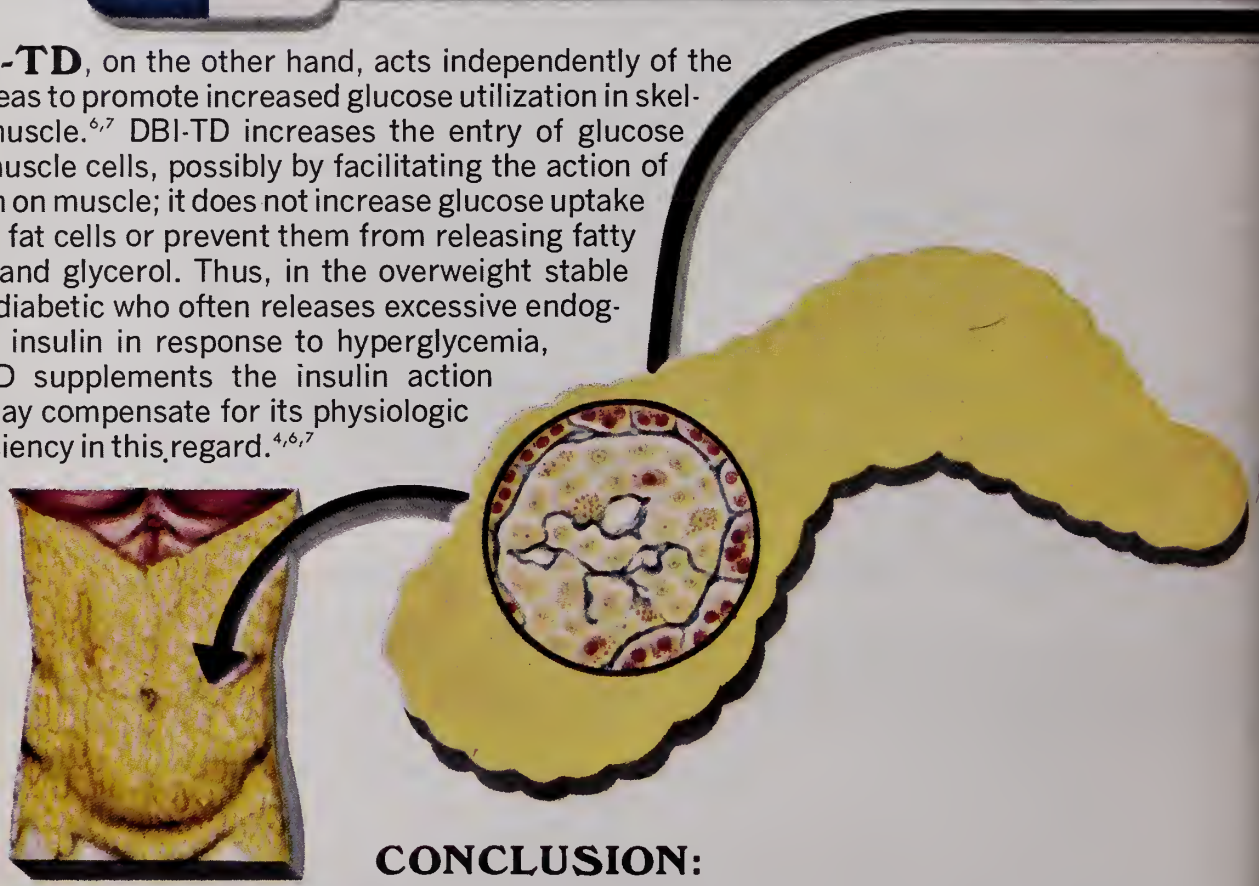
VOL. 60 ABRIL 1968 NUM. 4

DBI-TD Does Differ From the Sulfonylureas

SULFONYLUREAS stimulate insulin release by the pancreatic beta cells. Endogenous insulin is often present in excess in stable adult diabetics who are overweight.[1,2] This insulin is apparently inefficient in transporting glucose into skeletal muscle, although it retains its activity in adipose tissue.[3,4] Insulin is not only a potent lipogenic hormone, it is also antilipolytic (suppresses fat mobilization from tissues) and thus can contribute to weight gain.

DBI-TD

DBI-TD, on the other hand, acts independently of the pancreas to promote increased glucose utilization in skeletal muscle.[6,7] DBI-TD increases the entry of glucose into muscle cells, possibly by facilitating the action of insulin on muscle; it does not increase glucose uptake by the fat cells or prevent them from releasing fatty acids and glycerol. Thus, in the overweight stable adult diabetic who often releases excessive endogenous insulin in response to hyperglycemia, DBI-TD supplements the insulin action and may compensate for its physiologic inefficiency in this regard.[4,6,7]



CONCLUSION:

DBI-TD acts directly to enhance muscle glucose utilization, whereas sulfonylureas appear to depend upon a supply of insulin releasable from the patient's pancreas for their hypoglycemic effect. Unlike injected insulin or the endogenous insulin released under the stimulus of the sulfonylureas, DBI-TD does not promote the conversion of glucose to fat or prevent the mobilization of fatty acids from the adipose tissue depots of the body.



This is Why DBI-TD should be your Drug of First Choice for Most Stable Adult Diabetics

who are overweight and diet-unresponsive

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26 JUN 1968

DBI®-TD (phenformin HCl)

timed-disintegration capsules 50 mg.

ALONE among oral hypoglycemic agents... provides more benefits for most stable adult diabetics

- Lowers blood sugar
- Increases muscle glucose utilization
- Reduces insulin oversecretion
- Promotes gradual weight loss*

*Although anorexia has been suggested as a possible basis for weight loss, controlled studies do not support this. In nondiabetic subjects who are overweight, comparable doses of DBI-TD do not induce weight loss or lower blood sugar.

Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis (ketonuria without hyperglycemia) which must be differentiated from "insulin lack" ketosis which is accompanied by acidosis, and treated accordingly. Lactic acidosis has been reported in nondiabetics and diabetics treated with insulin, with diet, and with DBI. Question has arisen regarding possible contribution of DBI to lactic acidosis in patients with renal impairment and azotemia and also those with severe hypotension secondary to myocardial or bowel infarction. Periodic B.U.N. determination should be made when DBI is administered in the presence of chronic renal disease. DBI should not be used when there is significant azotemia. Any cardiovascular lesion that could result in severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also available:** DBI tablets 25 mg. Consult product brochure.

References: 1. Yalow, R.S. and Berson, S.A.: Diabetes 9:254, 1960. 2. Grodsky, G.M. et al.: Metabolism 12:278, 1963. 3. Gundersen, K. and Antoniades, H.: Proc. Soc. Exp. Biol. Med. 104:411, 1960. 4. Williams, R.H.: Textbook of Endocrinology, Ed. 3, Philadelphia, Saunders, 1962. 5. Gordon, E.S.: Advances Internal Med. 12:66, 1964. 6. Butterfield, W.J.H. and Whichelow, M.J.: Diabetes 11:281, 1962. 7. Searle, G.L. and Cavalieri, R.R.: Presented at 26th Ann. Meet. Amer. Diabetes Ass., Chicago, June 25-26, 1966.

U. S. Vitamin and Pharmaceutical Corporation, New York, New York 10017

Otro nuevo descubrimiento de Lakeside



cuando la depresión abruma

NORPRAMIN

(clorhidrato de desipramina)

el ANTIDEPRESIVO
no-sedante de acción rápida

vence el abatimiento, levanta el ánimo, restablece la confianza

La depresión frecuentemente se caracteriza por sentimientos de culpabilidad, inutilidad, desolación y privación. Estas manifestaciones, acompañadas de síntomas tales como insomnio, malestar, tristeza y recelo, responden rápidamente al NORPRAMIN (clorhidrato de desipramina). La mejoría generalmente se manifiesta 2 a 5 días después de iniciado el tratamiento; algunas veces antes. Los pacientes con sensibilidad comprobada a estimulantes del sistema nervioso central, pueden experimentar excitación al desaparecer su depresión; en estos casos se sugiere reducir la dosis o administrar simultáneamente tranquilizantes.

Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardiacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extraoiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

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ORGANO OFICIAL

Fundado en 1903

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Anuncios y Suscripciones:
El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

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Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

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QUE UNA AMPULA DE 5 cc. DE



IMFERON

(inyeccion de hierro dextran)

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PRODUCTOS PARA PACIENTES QUE UD. VE A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

¿Contento? ¡Si!

Porque soy fuerte y saludable gracias a

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Doctores y hospitales siempre pueden recomendar con confianza la LECHE EVAPORADA CARNATION por su probada reputación, calidad y frescura. La LECHE EVAPORADA CARNATION ha sido usada por generaciones en Puerto Rico porque significa bebés fuertes y saludables.



* Fernandito Castro Pavía ganador del Concurso del Bebé Saludable Carnation de 1965.

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doxycycline
New
from
Pfizer Research



Once-a-day dosage after the first day of therapy... lowest daily dose of any oral tetracycline*

Pfizer LABORATORIES DIVISION
New York, N.Y. 10017

after the first day—
The only one-dose-a-day oral broad-spectru antibiotic

Product Information

Actions: Vibramycin (doxycycline), a new broad-spectrum antibiotic, differs from o tetracyclines in its greater absorption from the gastrointestinal tract and its capab for once-a-day maintenance dosage. Also, in comparison with certain other tetracyclines, the absorption of Vibramycin is not notably diminished by the ingest of food or milk.

After discontinuance of therapy, effective antibacterial levels of Vibramycin are usually present for 24-36 hours.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkey

Indications: Vibramycin has been found to be clinically effective in the treatment a variety of bacterial infections of the respiratory and genitourinary tracts and soft-tissue infections. Since Vibramycin is a member of the tetracycline series, it n expected to be useful in the treatment of gastrointestinal, ophthalmic and other miscelloneous infections when caused by susceptible organisms.

Contraindications: Vibramycin is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: In patients with impaired renal function, reduce usual oral dosage and consider serum level determinations to avoid liver damage from excessive systemi accumulation.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although *in vitro* it binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infa receiving tetracyclines, which effect disappears rapidly on cessation of therapy.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, shoul utilized. In all cases in which concomitant syphilis is suspected, monthly serologic tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proc onycholysis and discoloration of the nails may rarely occur during tetracycline therapy, as with other antibiotics. If adverse reactions, individual idiosyncrasy, o allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutrope eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg. The maintenance dose may be administered as a single dose, or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infect of the urinary tract), 100 mg. every 12 hours is recommended.

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided int two doses, on subsequent days. For more severe infections, up to 2 mg./lb. of bo weight may be used. For children over 100 lbs., the usual adult dose should be us Therapy should be continued beyond the time that symptoms and fever have subs It should be noted, however, that effective antibacterial levels are usually preser for 24 to 36 hours following the discontinuation of Vibramycin.

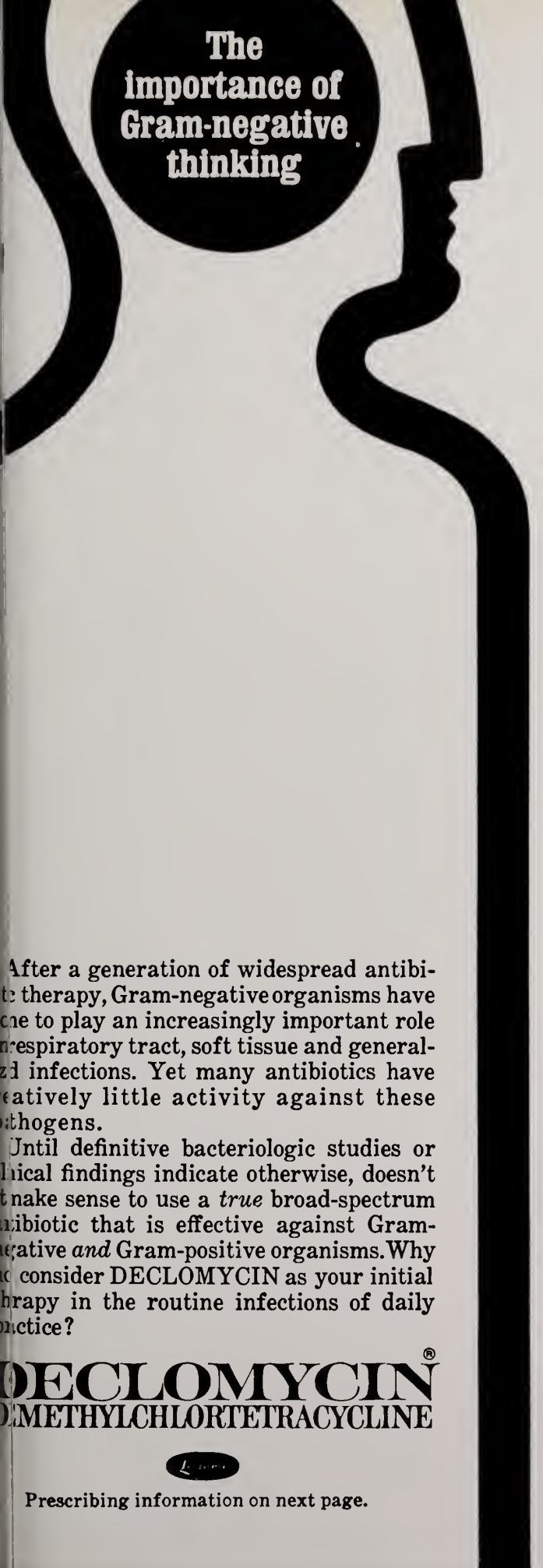
When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Aluminum hydroxide gel given with tetracycline antibiotics has been shown to decrease their absorption.

Supply: Vibramycin Hyclate (doxycyline hyclate) is available as capsules contair doxycycline hyclate equivalent to 50 mg. of doxycycline, bottles of 50.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powd for oral suspension containing when reconstituted doxycycline monohydrate equi to 25 mg. of doxycycline per 5 cc. (each teaspoonful), with a pleasant-tasting raspberry flavor, 2 oz. bottles.

More detailed professional information available on request.



After a generation of widespread antibi-
t: therapy, Gram-negative organisms have
cne to play an increasingly important role
n:espiratory tract, soft tissue and general-
zd infections. Yet many antibiotics have
eatively little activity against these
:thogens.

Until definitive bacteriologic studies or
lical findings indicate otherwise, doesn't
t nake sense to use a *true* broad-spectrum
ibiotic that is effective against Gram-
gative *and* Gram-positive organisms. Why
consider DECLOMYCIN as your initial
hrapy in the routine infections of daily
nctice?

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

Lederle

Prescribing information on next page.

For a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill.

True broad spectrum

DECLOMYCIN Demethylchlortetracycline should be equally or more effective than other tetracyclines when the offending organisms are tetracycline-sensitive.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth — dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; **Tablets:** film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

LEDERLE LABORATORIES, A Division of
American Cyanamid Company, Pearl River, New York

Lederle


Hairy sites where creams and ointments do not spread or penetrate readily.
Exposed areas where cosmetic considerations are important.

An invisible topical

for many dermatologic problems



See last page for contraindications, precautions and side effects.

Structurally unique topical steroid in propylene glycol vehicle produces rapid response in many dermatoses.

Synalar Solution produces rapid antiinflammatory, antipruritic action through its unique topical corticosteroid, fluocinolone acetonide. The propylene glycol vehicle provides additional benefits for therapy at problem sites where it is difficult to achieve contact between the lesion and medication—or where creams or ointments may make the lesions worse. Synalar Solution has proved particularly valuable in the symptomatic treatment of seborrheic dermatitis of the scalp, nasolabial folds, eyebrows, ears, and in flexural folds such as the axillae, inframammary, umbilical and anocrural areas. It has also been reported to achieve excellent results in the adjunctive management of atopic dermatitis, contact dermatitis, neurodermatitis, nummular eczema, psoriasis, and sweat retention syndromes in these problem sites.

Penetrates the hairy sites.

In many areas of the body, hair gets in the way of treating the underlying dermatitis. The propylene glycol vehicle of Synalar Solution permits penetration and dispersion at sites where creams and ointments do not readily penetrate. May be applied without matting of hair.

Ideal for moist or intertriginous areas.

Propylene glycol is strongly hygroscopic and is especially useful where sweat retention is a problem. Its low surface tension permits easy spreadability in difficult-to-treat body areas. A number of studies have also shown that propylene glycol has inherent antimicrobial activity.



Cosmetically acceptable for exposed areas.

The propylene glycol vehicle Synalar Solution possesses many useful cosmetic properties. Clear and greaseless, it is not sticky or messy, will not stain clothing or skin.

For exposed areas of the body where cosmetic appeal is important, Synalar Solution shows nothing but results.

Economical—a little goes a long way.

Because of the properties of propylene glycol and the milligram potency of fluocinolone acetonide, a small quantity of Synalar Solution goes a long way. Also, the prescription price of a 20 cc. plastic squeeze bottle of Synalar Solution is surprisingly low. Thus, your patients obtain economy with the proved efficacy of a potent, truly advanced topical corticosteroid.

Contraindications: Tuberculous, fungal, and most viral lesions of the skin (including herpes simplex, vaccinia, and varicella). Not for ophthalmic use. Contraindicated in individuals with a history of hypersensitivity to any of the components.

Precautions: In some patients with dry lesions, the solution may increase dryness, scaling, or itching. Application to denuded or fissured areas, such as genital or perianal sites, may produce a burning or stinging sensation. If this persists and dermatitis does not improve, discontinue medication. Although propylene glycol has antiseptic activity, there should be careful initial evaluation and follow-up of infected sites. Incomplete response or exacerbation of lesions may be due to true infection, which requires susceptibility testing and appropriate therapy. On the other hand, saprophytic or low grade infections may clear spontaneously under the influence of Synalar Solution alone. Where severe local infection or systemic infection exists, the use of systemic antibiotics should be considered, based on susceptibility testing. While topical steroids have not been reported to have adverse effect on pregnancy, the safety of their use on pregnant females has not absolutely been established. Therefore, they should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Side Effects: Side effects are not encountered ordinarily with topically applied corticosteroids. As with all drugs, however, a few patients may react unfavorably to Synalar under certain conditions.

Availability: Synalar (fluocinolone acetonide) Solution 0.01% in a propylene glycol vehicle with citric acid as preservative. 20 and 60 cc. plastic squeeze bottles. *Also available:* Synalar (fluocinolone acetonide) Cream 0.025%—5, 15 and 60 Gm. tubes and 425 Gm. jars. Cream 0.01%—15, 45 and 60 Gm. tubes and 120 Gm. jars. Ointment 0.025%—15 and 60 Gm. tubes. Neo-Synalar® (neomycin sulfate 0.5% [0.35% neomycin base], fluocinolone acetonide 0.025%) Cream—5, 15 and 60 Gm. tubes.

fluocinolone acetonide — an original steroid from

SYNTEX

LABORATORIES INC., PALO ALTO, CALIF.

Synalar®
(fluocinolone acetonide)
Solution
0.01%

An invisible topical





PIENSE EN SU MEDICO Y PIENSE EN LOS SUYOS

Adquiera Tranquilidad: Ingrese en la Triple S

Nadie es eternamente saludable. Es lógico suponer que, en cualquier momento, algunos de sus familiares —o usted mismo— requerirá atención médica y, quizás, hospitalización.

Como jefe de familia, usted se verá en la obligación de atender esa necesidad con mayor premura que las otras: casa, comida, ropa, vestidos y diversiones.

No espere ese momento; adquiera tranquilidad desde ahora con el plan de protección médico quirúrgico y de hospitalización de la Triple S (SSS). Económico, eficaz y simple.

Por una módica prima mensual —menos de lo que gasta en cosas menos importantes que la salud— usted se protege y protege a los suyos. La Triple S le ofrece servicios médicos, de hospitalización y dentales.

Por eso — le aseguramos— adquirir su tarjeta de la (SSS) es adquirir tranquilidad.

Miembro de la National Association of Blue Shield Plans

®

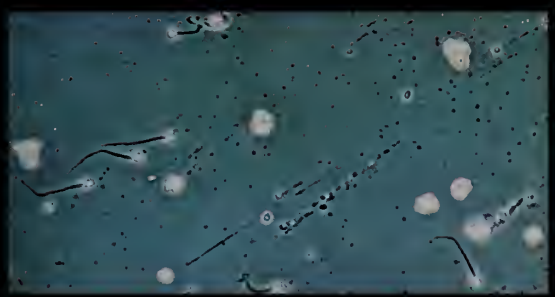
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

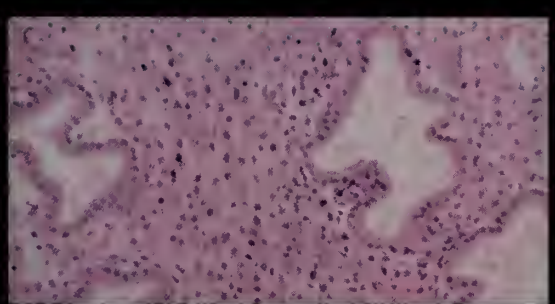
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.



Spermatozoa appear healthy, active, freemoving.

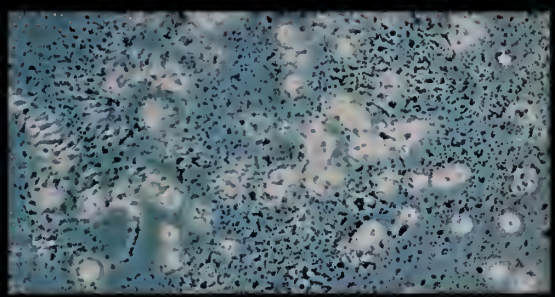


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

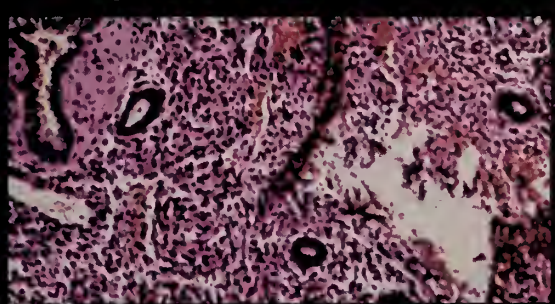
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



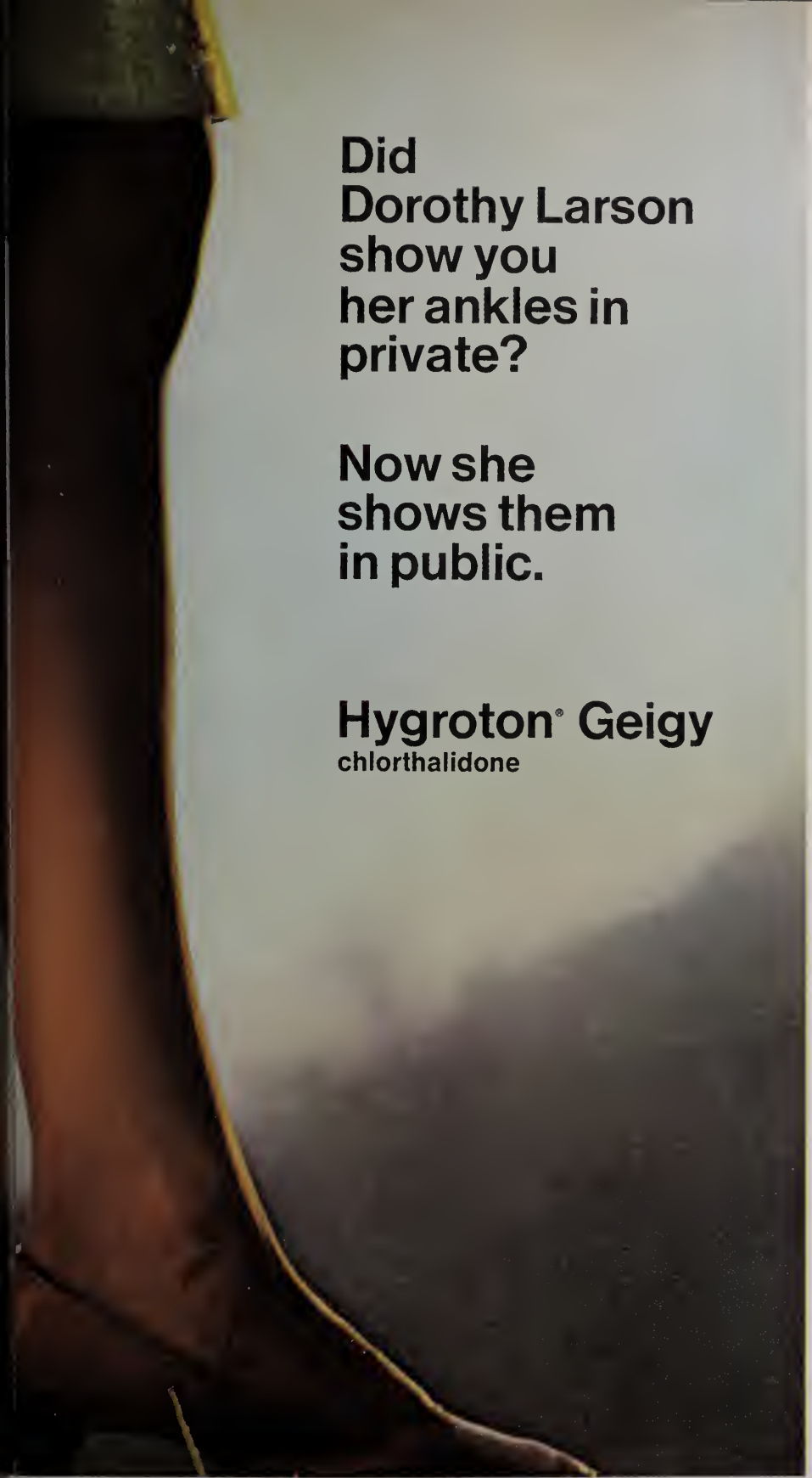
Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

Norinyl®-1
(norethindrone 1mg c mestranol 0.05mg) tablets

- new low dose of time-proved ingredients
- established norethindrone/mestranol ratio
- lower patient cost



Indications: Hypertension and many types of edema involving retention of salt and water.
Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.
Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Hygroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. Be
cause of the possibility of prog
sion of renal damage, periodic
determination of the BUN is in
cated. Discontinue if the BUN r
or liver dysfunction is aggravat
Hepatic coma may be precipita
Electrolyte imbalance, sodium
or potassium depletion may oc
If potassium depletion should
cur during therapy, Hygroton sh
be discontinued and potassium
supplements given, provided th



Did Dorothy Larson show you her ankles in private?

Now she shows them in public.

Hygroton® Geigy
chlorthalidone

Your office examination confirmed Mrs. Larson's ankle edema.

You prescribed Hygroton—to get rid of the edema.

And you found that Hygroton is not only effective; it frequently costs less than other equivalent therapy.

A nice way to treat the Mrs. Larsons in your practice.

Hygroton therapy may mean troublesome side effects for some patients. A summary of the prescribing information is shown below.

...t does not have marked oli-
...special care in cirrhosis or ...e ischemic heart disease and ...pients receiving corticoste-...d ACTH, or digitalis. Salt re-...on is not recommended.
...se Reactions: Nausea, gastric ...on, vomiting, anorexia, con-...on and cramping, dizziness, ...ess, restlessness, hyperglyc-..., hyperuricemia, headache, ...e cramps, orthostatic hypo-tension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.
Average Dosage: 50 or 100 mg. with breakfast daily or 100 mg. every other day.
Availability: White, single-scored tablets of 100 mg. and aqua tablets of 50 mg., in bottles of 100 and 1000.
(B)R46-230-D
For full details, please see the complete prescribing information.

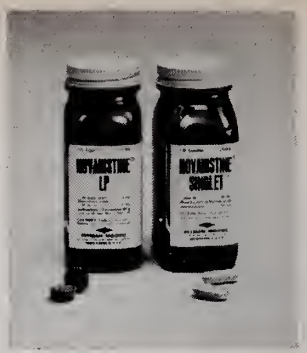
Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York 10502

HY-5576R

Some U.R.I. patients are more miserable than others.

That's why we make Novahistine® tablets in two different formulations.

And let you control the dosage.



Each Novahistine LP tablet contains phenylephrine hydrochloride, 25 mg.; and chlorpheniramine maleate, 4 mg.
Each Novahistine Singlet tablet contains phenylephrine hydrochloride, 40 mg.; chlorpheniramine maleate, 8 mg.; and acetaminophen, 500 mg.

With Novahistine LP tablets and Novahistine Singlet™ tablets you have the range and flexibility of decongestant dosage that lets you prescribe for the needs of the individual patient.

Novahistine LP tablets are most useful for relief of nasal congestion in patients without pain or fever. Novahistine Singlet tablets, which provide analgesic-antipyretic effect, as well as decongestant action, are indicated for upper respiratory infections accompanied by pain, aches and fever.

Whether you prescribe Novahistine LP or Novahistine Singlet, a total daily dose of 3 or 4 tablets will usually provide effective, continuous relief.

Use cautiously in patients with severe hypertension, diabetes mellitus, hyperthyroidism or urinary retention. Caution ambulatory patients that drowsiness may result.

DOW **PITMAN-MOORE** DIVISION OF THE DOW CHEMICAL COMPANY, INDIANAPOLIS

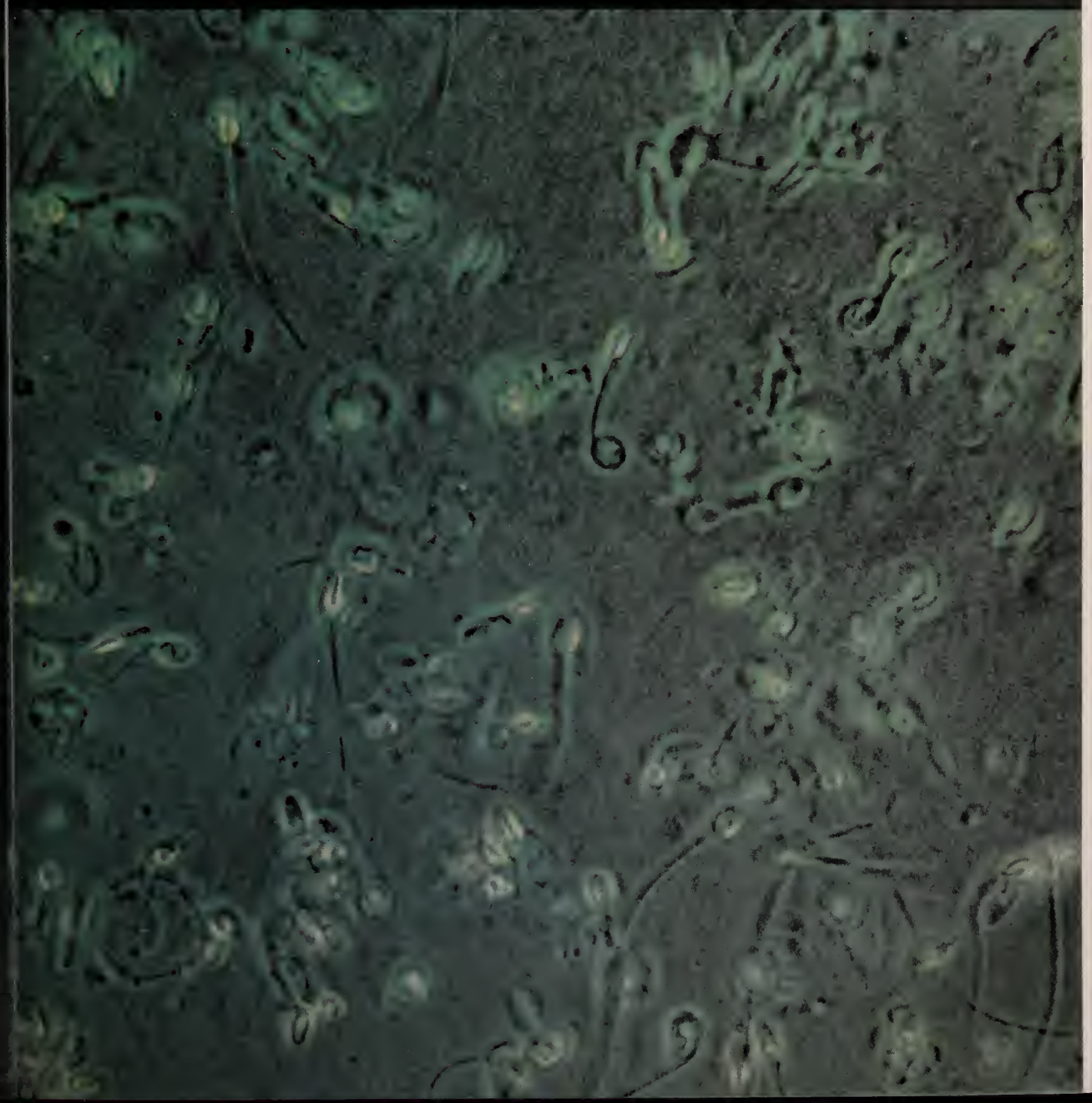


"Nothing else I've tried seems to work, so I decided to give you a crack at it."

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. c mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretions suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factors VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine and decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from
SYNTEX
LABORATORIES INC., PALO ALTO, CALIF.

CARCINOMA OF THE ESOPHAGUS
Experience at the San Juan V.A. Hospital

José I. Iglesias, MD
J. D. Pagán-Pagán, MD, FACS
Héctor M. Nadal, MD, FACS

Carcinoma of the esophagus in Puerto Rico accounts for 8% of all cancers in the male and 4% in the female. In the year 1960 Puerto Rico ranked first among 25 other countries in the age adjusted mortality for this disease. The incidence has been steadily increasing, showing the largest increase among all cancer sites locally. Martínez, from the Puerto Rico Cancer registry, has demonstrated that even after taking into consideration the increase and aging of the population, the number of patients with carcinoma of the esophagus has increased markedly during the past decade. This increase has been particularly significant in the male population (1, 2, 3). This trend has also been reflected in the number of patients seen with this disease at the Veterans Administration Hospital in San Juan, Puerto Rico. during the past 20 years.

Clinical Material and Results

The data presented here includes the analysis of 95 clinical records available from 117 patients found to have primary carcinoma of the esophagus during the years 1946 to 1966. Their age distribution is shown in Table I, the highest incidence being in the sixth decade. Most of the patients came from the southern and northeastern areas of the Island. Sixty-six of the patients were moderate to heavy smokers and 38 had a history of heavy alcohol intake. Six patients had previous or concomitant esophageal disease; two had esophagitis, one hiatal hernia, and three had esophageal varices. In 12% of the patients another primary tumor was recorded. Three of these had carcinoma of the prostate, which probably represents an age related coincidence. Three patients had associated oropharyngeal lesions.

TABLE I: AGE DISTRIBUTION

Age (Years)	No.
0 — 20	0
21 — 30	0
31 — 40	3
41 — 50	9
51 — 60	10
61 — 70	47
71 — Over	26

Dysphagia was the first manifestation of the disease in almost all of the patients (Table II). In some instances, this was

From the Surgical Service, Veterans Administration Hospital, San Juan, Puerto Rico and the University of Puerto Rico School of Medicine.

Presented at the Annual Meeting of the Puerto Rico Medical Association on November 18, 1967.

TABLE II: PRESENTING SYMPTOMS

Sympton	No.
Dysphagia	82
Epigastric pain	3
Regurgitation	3
Substernal pain	2
Hemathemesis	1
Neck mass	1
Fever	1
Anorexia	1
Cachexia	1

accompanied by pain upon swallowing, that is, odynophagia. Other associated symptoms were anorexia, hoarseness, cough, weakness and fever. Regurgitation and weight loss are late manifestations of the disease and unfortunately were usually present when the patient was seen at the hospital. By the time of diagnosis most patients had lost considerable weight and some were cachectic. The majority of the patients had had symptoms for over three months at the time of diagnosis.

Few patients had evidence of metastatic disease on physical examination. Supraclavicular lymph nodes were palpable in only five patients and an epigastric mass was found in four.

The diagnosis was made by radiological examinations in nearly all patients. Characteristically the esophagogram showed deformity or irregularity of the esophageal lumen resulting in various filling defects at different levels (Figures 1, 2, 3). In only one patient was a false negative report obtained. This was a very small tumor diagnosed incidentally during esophagos-

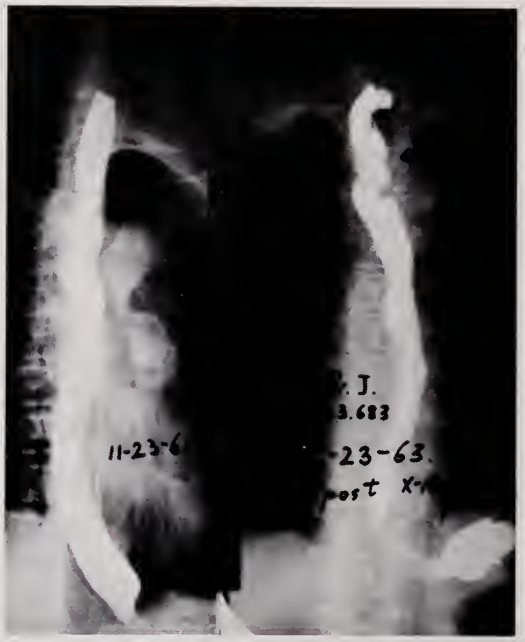


Fig. 1: Esophagogram showing upper thoracic lesion.



Fig. 2: Esophagogram showing middle thoracic lesion.



Fig. 3: Esophagogram showing lower thoracic lesion.

copic examination for esophageal varices. In another patient the tumor was detected at the time of high gastric resection for adenocarcinoma of the stomach. Esophagoscopy confirmed the radiological impression and enabled us to obtain histological proof in 95% of the cases.

All of the tumors were epidermoid carcinomas, and in two of them a pseudosarcomatous stroma was present. All adenocarcinomas of the cardioesophageal area were excluded as they were probably all of gastric origin. The location of tumors is shown in Table III. The level recorded is that of the uppermost extent of the tumor as determined by esophagoscopy or by esophagography. In 46% of the patients the lesions were located in the middle third of the esophagus; 29% had lower third lesions; 15% had upper third lesions; and

TABLE III: LEVEL OF THE LESION

Level	No.	Distance From Teeth
Cervical	4	15-20 cm
Upper thoracic	15	20-26 cm
Middle thoracic	45	26-36 cm
Lower thoracic	28	36-45 cm
Unknown	3	

in 4% the lesions were in the cervical esophagus.

Of the 95 patients, 10 received only symptomatic treatment because of far advanced disease. An additional seven were explored, found unresectable, and only supportive treatment was given thereafter. Forty-three were treated with resection as the primary method of therapy. Twenty-six cases not submitted to surgery received radiotherapy. Another three patients who were explored and found unresectable also received palliative radiotherapy. In six patients surgery and radiotherapy were combined in an effort to improve the prognosis. Four of these patients received irradiation before and two following resection (Table IV). In the resected cases,

TABLE IV: TREATMENT

Treatment	No.
Radiotherapy alone	29*
Surgery alone	43
Surgery and radiotherapy	6
Exploration and symptomatic	7
Supportive alone	10

**3 were found unresectable and then received a full course of X-ray therapy*

an esophagogastrostomy has been used almost routinely to re-establish the continuity of the gastrointestinal tract (Figure 4a, b). A pyloroplasty is added to over-



Fig. 4 a: Esophagogram demonstrating an esophagogastrostomy.

come the secondary gastric atony produced by the incidental vagotomy. Recently a colon interposition has been preferred for high lying tumors. This last method has also been used to bypass the obstruction as a palliative measure. We prefer the right colon, but the left colon can be utilized for the same purpose (Figure 5a, b). A Mackler tube was placed in one patient for palliation following a full course of radiotherapy (Figure 6). This patient had excellent palliation since he lived slightly over a year and was swallowing well except for a few episodes of acute obstruction which were promptly relieved by esophagoscopic extraction of solid food particles.

Resection was carried out in 49 of the 59 surgically explored patients. This is a very high resectability rate as compared

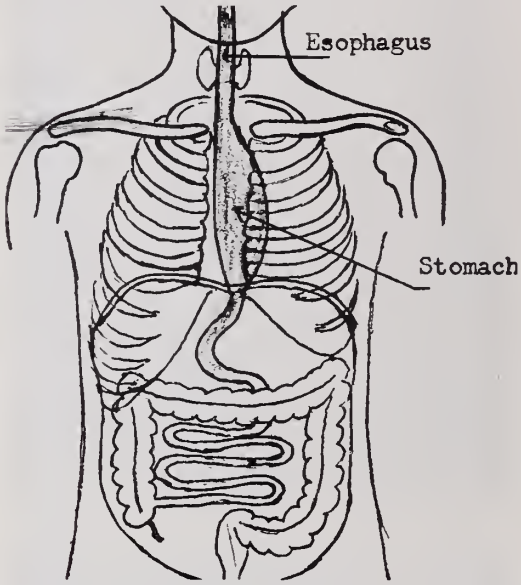


Fig. 4 b: Graphic representation of an esophagogastrostomy.

with other institutions (4, 5, 6, 7, 8, 9) (Table V). Twenty-two of the resected cases were judged to have curative procedure at the time of operation. The remaining resections were considered palliative in nature. Twenty-four of the resected cases were in the middle third; 18 were in the lower third and 7 in the upper third of the esophagus. No cervical lesions were resected.

The results are summarized in Table VI. Of the 29 patients receiving radiotherapy, 6 were alive at the end of one year and 1 has survived nine years. It is interesting to note that the latter patient (case 3) was explored and found to have an infiltrating unresectable tumor. He was then treated with 5,680 Roentgens of



Fig. 5 a: Esophagogram demonstrating a colon interposition, lateral view.

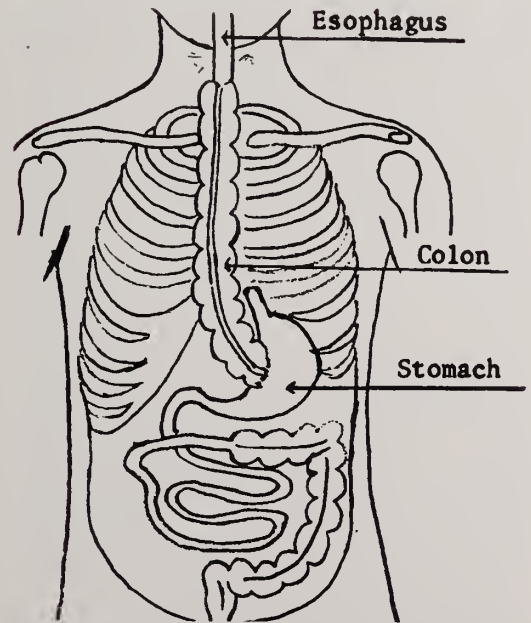


Fig. 5 b: Graphic representation of right colon interposition.



Fig. 6: Esophagogram showing the Mackler tube in place.

TABLE V: RESECTABILITY. RATE

Series		%
Ellis (Mayo Clinic)		37
Marcial (Puerto Rico Oncologic Hosp., San Juan)		11
Moss (Review of the literature)	6.4	43
Parker and Gregorie (Med. College South Carolina)		60
Postlethwait (Duke Univ. North Carolina)		21
Saegesser and Hofstetter (Switzerland)		38
San Juan V.A. Hospital		83

telecobalt and he is still alive without evidence of disease. Resection alone was performed in 43 patients, 13 of whom were

TABLE VI: RESULTS OF TREATMENT

Treatment	No. of Patients by Site		1-Yr. Survivals		5 Yr. Survivals	
Radiotherapy	Cervical	3	Cervical	1		
	Upper	6	Upper	3		
	Middle	13	Middle	2	Middle	1
	Lower	6				
	Unknown	1				
	Total	29	Total	6 (20.7%)	Total	1* (7.1%)
Surgery	Upper	6	Upper	1		
	Middle	21	Middle	7	Middle	3
	Lower	16	Lower	5		
	Total	43	Total	13 (30.2%)	Total	3** (9.0%)
Resection followed by radiotherapy	Middle	1				
	Lower	1	Lower	1		
	Total	2	Total	1		
Radiotherapy followed by resection	Upper	1	Upper	1		
	Middle	2	Lower	1	None	
	Lower	1				
	Total	4	Total	2		
Symptomatic only	Cervical	1				
	Upper	2				
	Middle	8	None		None	
	Lower	4				
	Unknown	2				
	Total	17				

* *One out of 14 that qualified for five-year evaluation.*

** *Three out of 31 that qualified for five-year evaluation. Resectability rate —83%. Operative mortality —33%. Over all five-year survival irrespective of treatment is 4.2%.*

alive at the end of one year and 3 survived five years or more. Two (case 3 and 2) are still alive 10 and 12 years respectively after resection. One survived 5½ years after resection and died three months after a secondary operation for removal of the remaining portion of the esophagus - with recurrent tumor at the site of anastomosis. These three patients had middle third lesions. Of the six patients receiving radiotherapy either pre or post resection, three were alive at the end of one year, and one of them is still alive two years after combined therapy. This group is being followed closely to see if this trend continues into the five-year period. No conclusions can be drawn at the present time because of the small sample and short follow-up.

The surgical mortality was 33%. This was higher than most of the published mortality statistics (5, 8, 9, 10, 11, 12)

(Table I). This may be a reflection of the aggressive approach as demonstrated by the high resectability rate.

TABLE VII: OPERATIVE MORTALITY, RESECTED CASES

Series	%
Boyd and Adams	20
Kay (Medical College of Virginia)	40
Lortat-Jacob (Paris, France)	31
Marcial (Puerto Rico Oncologic Hospital, San Juan)	30
Postlethwait (Duke Univ., North Carolina)	25
Saegesser and Hofstetter (Switzerland)	26
San Juan V.A. Hospital	33

Case Reports

Case 1: A 45-year-old patient admitted on June 15, 1958, with a six-month history of progressive dysphagia until he became totally obstructed fifteen days prior to admission. He was reported to be a heavy smoker for about 30 years and only an occasional drinker. Physical examination was essentially negative except for evidence of weight loss and dehydration. Esophagogram and esophagoscopy with biopsy demonstrated the presence of an epidermoid carcinoma of the middle third of the esophagus (Figure 7.).

On June 23, 1958, esophagectomy and esophagogastrostomy was performed A large tumor of the middle third of the esophagus occupying an area under the aortic arch and extending to the level of the left inferior pulmonary vein, was resected. The tumor measured about 6 cm in length. Histologic examination revealed a well differentiated, infiltrative squamous cell carcinoma. The proximal and distal lines of resection were free of tumor and there was no evidence of metastases in the paraesophageal and posterior mediastinal lymph nodes examined.

At the time of Cholecystectomy, performed in



Fig. 7: Pre and post operative esophagograms —(Case 1) showing middle third lesion; and functioning esophagogastrectomy. Extrinsic pressure at the mesial aspects of the stomach is noted unchanged since examinations of March 3, 1961.

February 1966, there was no evidence of intraperitoneal metastasis. This patient is still alive without evidence of active disease ten years after initial diagnosis.

Coment: It is interesting to note that even a large tumor like this may be compatible with long survival if it is confined to the esophagus. There were no positive metastatic lymph nodes in this case.

Case 2: A 52-year-old patient admitted to this hospital on June 29, 1955, with hematemesis. Since the age of 17 this patient had been a heavy drinker. Three months prior to admission he developed epigastric pain and occasional melena. Physical examination was essentially negative except for hepatomegaly.

Esophagogram and G.I. series were reported negative. Esophagoscopy was performed revealing the presence of a small tumor arising from the lateral wall of the esophagus at the junction of the upper and middle third. No varices were seen at the lower esophagus. Subsequently another esophagogram demonstrated the lesion (Figure 8). Biopsy was reported as epidermoid carcinoma.

On July 26, 1955, esophagectomy and esaphagogastrostomy were performed At the time of the operation a 1.5-2 cm tumor was palpable within the esophageal wall at the level of the arch of the aorta. Histologically the tumor was limited to the mucosal layer of the esophagus.

Since then he has had several admissions to this hospital, the last one being in January 1965, because of heart failure. He has been free of tumor as demonstrated by repeated esophagoscopies and esophagograms. He is still alive over 12 years since diagnosis and treatment.

Comment: This case emphasizes the importance of early diagnosis if survival is to be prolonged.

Case 3: A 64-year-old male patient was admitted in February 1959, complaining of dysphagia and a 20 lbs. weight loss. He had been a heavy

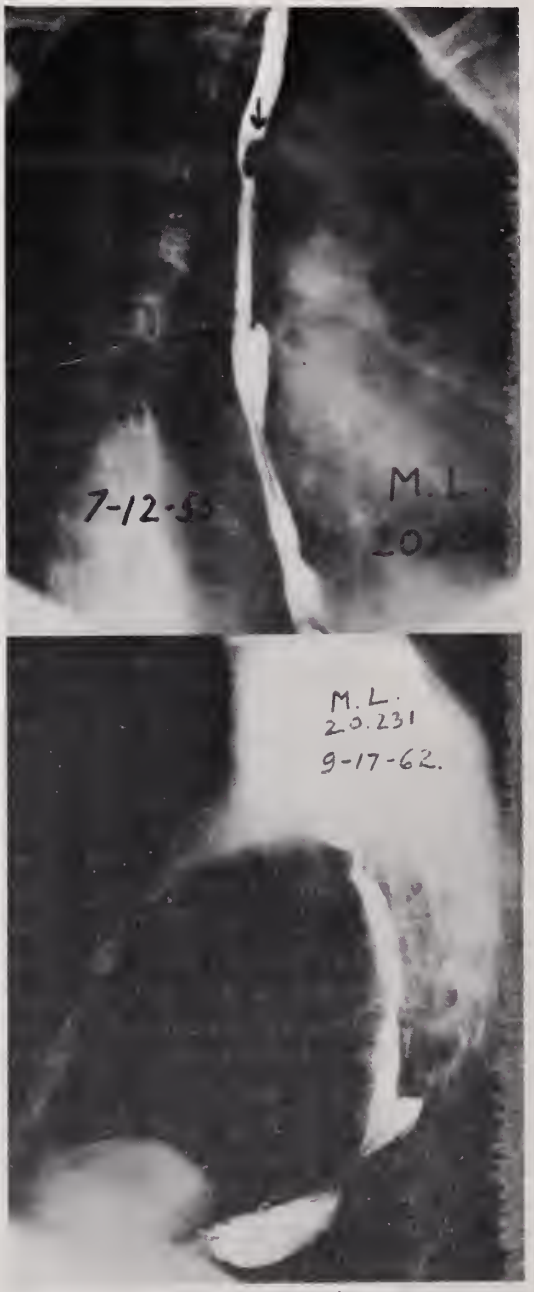


Fig. 8: Pre and post operative esophagograms — (Case 2) showing an ovoid lesion, anterior wall of the esophagus; and functioning esophagogastrostomy.

smoker since the age of 8 (two packages of cigarettes daily).

Physical examination was essentially negative. Esophagogram showed stenosing deformity at the middle third of the esophagus (Figure 9). Esophagoscopic examination and biopsy confirmed the clinical and radiological impression of epidermoid carcinoma of the middle third of the esophagus.

A temporary gastrostomy was performed to improve the nutritional status of the patient. On March 31, 1959, an exploratory thoracotomy was performed. An inoperable carcinoma at the middle third of the esophagus measuring 2.5 cm in length and fixed to the hilus of the left lung at the root of the left main bronchus was found. Biopsy of two periapical lymph nodes demonstrated metastatic epidermoid carcinoma.

After an uneventful post operative course the patient was treated with 5,600 Roentgens of cobalt therapy with marked improvement of his symptoms.

The patient's present complaints are limited to dysphagia secondary to a partial stenosis at side of previous tumor. Esophagogram on January 1, 1968, showed evidence of a short segment of narrowing in the mid-thoracic esophagus at the level of the aortic arch.

Comment: This case illustrates successful radiotherapeutic control in spite of a large infiltrating tumor with regional metastases deemed unresectable at thoracotomy.

Discussion

Martínez (1, 2, 3) encountered that carcinoma of the esophagus in Puerto Rico is more prevalent in the Western Health District. Most of the cases in the present series, however, came from the southern and northeastern areas of the Island.

Several factors have been incriminated in the literature (13, 14, 15, 16) as related to the etiology of carcinoma of the esophagus, namely: dietary deficiencies, al-





Fig. 9: Pre-treatment and follow-up esophagograms — (Case 3) demonstrating stenosing lesion of the esophagus (please disregard the artefacts); and short segment of narrowing at site of previously treated tumor. There is an old thoracotomy and a dense infiltrate, RUL, most likely secondary to irradiation.

cohol, tobacco, hot or spicy food, ethnological factors, and others. Apart from the carcinogenic effect of prolonged contact with irritating agents, there is little to support any single factor. Recently this has been emphasized in the case histories and a greater association with heavy smoking and drinking has been observed. It has been noted that the consumption of alcoholic beverages and cigarette smoking has increased markedly in Puerto Rico in the last 2½ decades. This parallels the increase in number of cases of carcinoma of esophagus (2) seen in the Island.

Awareness of the early manifestations of the disease and a high degree of suspicion are important in order to correctly evaluate early symptoms which might seem trivial. Vague substernal fullness or pressure or mild disturbance in swallowing are often the first manifestation of an esophageal neoplasm. Early diagnosis and treatment offers the best prognosis, and cannot be overemphasized. Dysphagia should always be regarded as caused by an esophageal tumor until proven otherwise, and requires radiological and esophagoscopic evaluation. With the use of the flexible esophagoscope we foresee a reduction in morbidity of esophagoscopic examination. Thus, there will be a more liberal and widespread use of this diagnostic procedure in the older age group with vague esophagogastric symptoms, particularly if they are heavy smokers and drinkers.

Due to the anatomical relations of the esophagus, tumors in this organ tend to invade very rapidly the surrounding tissues and important intrathoracic structures and metastases occur early to the mediastinal lymph nodes. Some authors state that if the tumor extends for more than 5 cm in length the probability of lymph node involvement is almost 100% (5). Most of the patients in this series had tumors extending from 5-6 cm in length by the time that the diagnosis was established.

Surgery and radiation are the only two effective methods of treatment. At the Veterans Administration Hospital all patients who did not show evidence of extraesophageal disease and were fair surgical risks were explored. We believe that resection gives the quickest palliation and an opportunity, although small, for cure. The mortality of exploration, however, is high because of the poor nutritional state of the patients. Palliation is aimed primarily at restoring the ability to swallow not only food but the patient's own saliva. Regurgitation and aspiration of saliva accounts for the bronchopneumonia that frequently complicates the course of this disease. Gastrostomy alone does not prevent this, and is therefore not a good method of palliation.

The results of treatment of carcinoma of the esophagus should be evaluated in two major parameters, namely survival and palliation obtained. In general the best palliation and best survival rate were obtained in those patients subjected to resection of the tumor. Survival is best measured at the end of one year since the number of patients surviving five years or more is very low. Six of the 29 patients treated with radiotherapy alone were alive one year after treatment. Thirteen of the 43 patients treated by resection were alive one year after treatment. Only four patients survived more than five years, three following resection and one following cobalt therapy. The overall five-year survival is 4.2%.

In most of the resected cases and in all long-term survivals in this series, the lesions were located in the middle third of the esophagus rather than the lower third. None of the patients with lower third lesions survived five years irrespective of treatment. All of the long term survivals had middle third lesions, two are still alive 10 and 12 years after resection, and one is alive 9 years after cobalt therapy.

The beneficial effects of preoperative irradiation has been reported (7, 18, 19). This modality of treatment is said to improve the resectability rate and the long term survival. Its greatest advocate is Nakayama and his associates from Japan. They administer 2,000 Roentgen of supervoltage irradiation in three days. Resection is performed within the first week after X-ray therapy. Their reports mention an increase in the three year survival rate from 6.8% for their patients treated with irradiation alone and 21.7% for those treated with resection only, to 44% for those patients using this combined method (18). The use of preoperative irradiation seems promising and further evaluation should be carried out.

Summary

Ninety-five patients found to have carcinoma of the esophagus during the past 20 years at the Veterans Administration Hospital, San Juan, Puerto Rico, were analyzed. Surgical resection offered the best palliation and a better although small chance for cure. The resectability rate is particularly high, 83%. The surgical mortality is 33%. The one-year survival rate was 30.2% for the resected cases and 20.7% for the radiotherapy treated cases. Of the 67 patients eligible for the five-year evaluation 4 survived five years or more, three after resection and one after irradiation. The overall five-year survival rate is 4.2%, which confirms the poor prognosis encountered with this disease around the world. The combination of surgery and radiotherapy seems promising. The case reports of the three patients with prolonged survival which are still alive are presented.

Resumen

Los historiales clínicos de 95 pacientes que fueron diagnosticados de cáncer de esófago en los últimos 20 años en el Hospital de la Administración de Veteranos, San Juan, Puerto Rico, fueron revisados. La resección quirúrgica del tumor ofreció la mejor paliación y la mayor oportunidad, aunque pequeña, de curación. El porcentaje de resectabilidad fue marcadamente alto, 83%. La mortalidad quirúrgica fue de 33%. La supervivencia al cabo de un año fue de 30.2% para los casos resecados y de 20.7% para aquellos que recibieron radioterapia. De los 67 pacientes que calificaban para la evaluación de cinco años, cuatro sobrevivieron cinco años o más, tres después de resección y uno luego de irradiación. La supervivencia total de cinco años fue solamente de 4.2% lo que confirma el mal pronóstico de esta enfermedad en el mundo entero. La combinación de cirigía precedida por radioterapia en casos seleccionados está bajo estudio. Los casos que han sobrevivido más de cinco años y que todavía están vivos fueron presentados.

Acknowlegements

Dr. Laszlo Ehrlich, Chief, X-Ray Service, is

responsible for the interpretation of the roentgen studies.

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IRON (^{59}Fe) BINDING CAPACITY IN THE DIAGNOSIS OF ANEMIAS

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R. Bernabe-Prida, BS

Iron binding protein, also called transferrin or sideophilin, plays a central role in the esentially closed cycle of iron transport in the body (1). The systems of iron transfer, in some of which transferrin plays an important role, include gastrointestinal absorption, erythropoiesis and erythrocyte destruction.

Although it was formerly thought that the degree of saturation of transferrin with iron regulated the facility of absorption of iron from the duodenum and proximal jejunum, experiments by Wheby (2) and others have shown that this is not an important factor. Iron is absorbed and deposited in the liver in its initial flow thru it, even in the absence of transferrin. In congenital atransferremia as described by Heilmeyer (3), iron absorption proceeds normally. Transferrin is important in the subsequent transport of iron from the liver to other tissues.

Iron utilized in the production of hemoglobin in erytroblasts is apparently obtained thru two processes. Transferrin is one of these sources, serving as a true transport protein which becomes fixed transiently to the cellular membrane where iron is yielded (1, 4). Alternately iron is obtained by erythroblasts from reticulum cells ("nurse cells") in the bone marrow which are rich in ferritin, another storage iron-protein complex (5).

Transferrin is also important in the transport of iron resulting from the breakdown of erythrocytes in the reticuloendothelial system particularly in the spleen and liver to the bone marrow and other tissues for utilization.

The physico-chemical nature of iron-binding protein has been extensively studied. It has been found to locate in Cohn's fraction 1V7 (4). On electrophoresis it behaves as a B_1 globulin. Its molecular weight is approximately 90,000 which is somewhat larger than that of albumin. On Sephadex fractionation it forms a peak just to the left of albumin. (6). Each protein molecule holds 2 Fe+++ atoms when fully saturated. Its plasma concentration is approximately 0.26 g/100 ml, thus constituting about 3% of plasma proteins (4).

Since direct determination of transferrin is only possible by rather involved immunochemical methods, its level in plasma is determined for clinical purposes indirectly by determination of the amount of iron bound to it. As only minute

Presented at the Annual Meeting, Puerto Rico Medical Association, San Juan, Puerto Rico, November 17, 1967.

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amounts of iron are present unattached in the blood, determination of the plasma iron level plus the additional iron which is needed to completely saturate the available protein gives an index of the total concentration of iron binding protein. Levels are thus expressed as μg Fe bound per volume unit of plasma.

Determination of plasma iron depends on the removal of iron from siderophilin usually by treatment with acid or heating and the production of color by coupling it, after reduction to ferrous form, to a,a-dipyridil, thiocyanate, or other appropriate compound.

Determination of iron-binding protein can be carried out in several ways. The spectrophotometric methods most commonly used involve the addition of a known excess of an iron salt in solution to the sample. The unbound iron is then measured by complexing it with a color reagent (7), or the excess iron is removed in various ways from the solution and an iron estimation is carried out on the saturated plasma (8). Peters (9) and Bothwell (10) introduced the used of ^{59}Fe into the latter type of procedure and employed an anion exchange resin to remove the unbound iron. The results of the latter method are comparable to the colorimetric ones and have the advantage of simplicity, speed and avoidance of interference by other colored substances in the plasma.

The present study is a review of our experience with the determination of unsaturated iron binding capacity using the above principle where the use of a polyether foam sponge to hold the ion exchange resin facilitates the removal of iron from solution. Studies using this method have been reported by Koepke (11) and Burrows (12) who compared it to colorimetric methods.

Materials and Methods

A group of 24 healthy male hospital employees ranging in age from 25 to 64 years was chosen as the normal group.

All patients studied were male, ranging in age from 22 to 83 years. The majority of them had anemia of various etiologies. The plasma iron (PI) and unsaturated iron binding capacity (UIBC) were part of the diagnostic work-up which included hemoglobin, hematocrit, leukocyte and erythrocyte counts and, when indicated, bone marrow examination, reticulocyte count; serum lactic acid dehydrogenase, serum proteins, stool guaiac and roentgen examinations of the gastro-intestinal tract. The results of treatment with specific agents such as iron, vitamin B_{12} and folic acid were noted upon review of the patient's records. When the cause of the anemia was not apparent by the time of discharge, the case was not included in the study.

Plasma iron (PI) was determined in duplicate using heating at 90-95º and TCA for separation of iron and KSCN with potassium persulfate for the production of color. Readings were done at 480 mμ in a Hitachi Perkin-Elmer spectrophotometer. Iron-free glassware and reagents were used throughout. When determinations were not carried out the same day, plasma was separated and stored at -10°C.

Unsaturated iron binding capacity (UIBC) was performed using radioactive iron (^{59}Fe) along with a polyether foam sponge in which is embedded a finely divided ion exchange resin, Amberlite IRA-400 type. This is the chloride form of a strongly basic anion exchange resin. The materials necessary for each test are supplied in the form of a kit (13). The plastic stopper (containing the resin-sponge) was removed from the plastic tube supplied with the kit, and the unstoppered tube was centrifuged for one minute to force all radioactive fluid to the bottom of the tube. Exactly 1 ml of the patient's serum (previously warmed to room temperature) was transferred into the plastic tube. The tube was swirled to insure uniform mixing and incubated for 10 minutes.

The resin-sponge was then pushed down into the liquid and the air expelled by compressing the sponge five times with the plunger. The plunger was removed allowing as much serum as possible to drain back into the plastic tube. Incubation for 60 minutes at 37°C was carried out. During incubation the radioactivity of the tube was counted in the well-type scintillation counter for one minute or 10,000 counts (whichever occurred first).

After incubation, the sponge was washed with distilled water. The liquid from the tube and resin-sponge was aspirated by means of the aspirator tip provided in the kit. Two or 3 ml of distilled water were added to the tube. The resin-sponge was compressed two or three times with the plunger and the wash water aspirated. Radioactivity remaining in the resin sponge was then counted.

The serum uptake was expressed as unsaturated (latent) iron-binding capacity:

$$\text{(original NCM)} - (1.05)\ \text{(Sponge NCM)}$$

$$\text{Original NCM}$$

$$X\ \mu g\ Fe\ added\ X\ 100 = \mu g\ Fe/100\ ml$$

The "μg added" can be read from the package label. The factor 1.05 is equal to 1% 0.95, This correction is necessary because the sponge takes up 95% of the iron not bound to the serum.

One sample from a normal subject was examined 9 times to determine the reproducibility of the results.

Values for PI and UIBC are expressed as μg Fe/100 ml of plasma.

Results

The data obtained in the various groups of patients is summarized in Table I and Figures 1, 2, 3 and 4.

Among 24 normal males examined, PI ranged from 50 to 141 μg/100 ml (average, 91 μg/100 ml. UIBC varied from 210 to 370 with an average of 128 μg Fe/100 ml. Saturation of transferrin varied from 15.8 to 38.9%, averaging 24.3%.

Nine determinations done simultaneously in one plasma sample varied from 253 to 312 μg/100 ml (mean ± SD = 275 ± 18).

Plasma iron among 26 patients with *iron deficiency anemia* due to blood loss ranged from 6 up to 94 μg/100 ml (aver-

TABLE I: PLASMA IRON AND UNSATURATED BINDING CAPACITY

Group	No.	Hemoglobin g/100 ml	PI μg/100 ml	UIBC μg Fe/100 ml	Saturation %
Normal	24	—	91 (50 - 141)	281 (210 - 370)	24.3 (15.8 - 38.9)
Hypochromic anemia	26	9.6 (5.0 - 12.8)	40 (6 - 94) *< .001*	410 (323 - 544) *< .001*	9.2 (3.1 - 18.4) *< .001*
Megaloblastic anemia	10	8.4 (4.0 - 11.2)	109 (35 - 192)	224 (130 - 370)	32.9 (15.7 - 48.7)
Renal diseases	10	9.4 (6.1 - 12)	71 (57 - 125)	246 (123 - 358)	29.9 (18.5 - 39.3)
Cancer	6	9.6 (7.6 - 11.2)	135 (50 - 199)	206 (120 - 295)	38.4 (14.6 - 60.7)
Collagen diseases	5	10.7 (9.4 - 11.8)	58 (50 - 90)	255 (219 - 279)	18.2 (10.7 - 25.2)
Infection, chronic	5	10.9 (10.6 - 11.8)	70 (37.6 - 86)	271 (197 - 306)	20.9 (10.9 - 24.8)
Cirrhosis, liver	7	9.7 (7.8 - 12)	56 (5 - 94)	243 (176 - 367)	18.6 (*< 1.6 - 34.8*)
Hepatitis	6	13.6 (11.2 - 15.2)	172 (141 - 265)	234 (103 - 327)	44.9 (33.8 - 62.5)

Mean and range of values (in parenthesis) is given for each group. Statistical significance of difference from the normal (P) for values in hypochromic anemia is shown in italics.

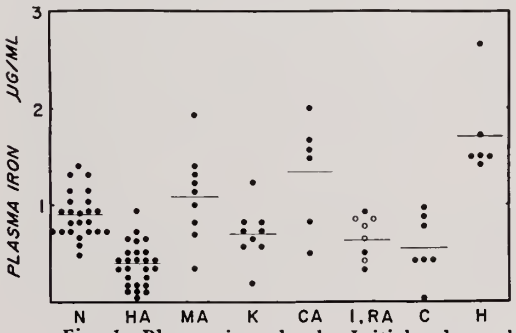


Fig. 1: Plasma iron levels. Initials along the ordinate in this and figures 2, 3 and 4 identify each diagnostic group as follows: N = normal; HA = hipochromic anemia; MA = megaloblastic anemia; K = renal diseases; CA = cancer; I = infections; RA = rheumatoid arthritis and other collagen disease (circles); C = cirrhosis of the liver; H = infectious hepatitis.

age, 40 μg). In only 2 subjects were values above 70 μg found. The UIBC ranged from 323 to 544 μg Fe/100 ml. The average value was 410 μg with only 3 cases showing levels below 350 μg.

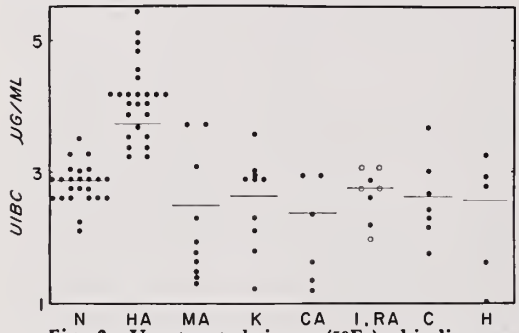


Fig. 2: Unsaturated iron (^{59}Fe) binding capacity.

The calculated values for saturation of transferrin averaged 9.2% with extreme values of 3.1 and 18.4%. There were three patients in this group whose transferrin iron saturation was above 15%. One of these, whose UIBC was 323 μg and who had the highest saturation value in the group, had had gastrectomy for duodenal ulcer and presently had a carcinoma of the esophagus. Bone marrow iron was detected in only 1 of 7 cases where this examination was done.

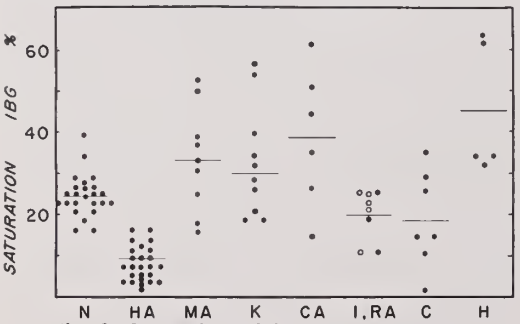


Fig. 3: Saturation of iron binding globulin.

Patients with *megaloblastic anemia,* on the other hand, had PI levels usually in the normal range or above. They ranged from 35 to 192 μg/100 ml, but only one value, in a patient with nutritional megaloblastic anemia, was below 69 μg/100 ml. UIBC varied from 130-370 (average, 224) μg Fe/100 ml. Percentage tranferrin saturation ranged from 15.7 to 48.7% with an average of 32.9%. Bone marrow smears showed abundant iron content in all except one where the preparation was not satisfactory.

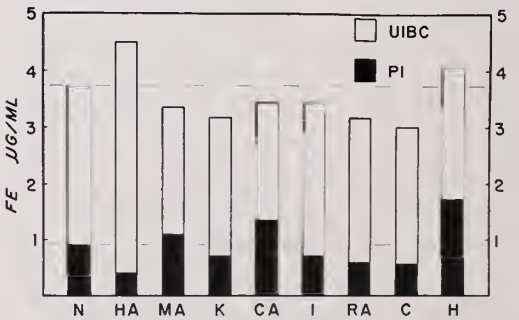


Fig. 4: Average values for plasma iron and unsaturated iron binding capacity. Broken line indicates mean normal values.

Among the group of 10 patients with *renal diseases* associated with anemia, the level of PI was quite variable, averaging 71 μg/100 ml. UIBC ranged from 123 to 358 μg/100 ml (average, 246 μg). Saturation varied from 18.5 to 39.3%, averaging 29.9%. The bone marrow, when examined, usually showed adequate iron stores.

The group labelled *"cancer"* included 1 case with carcinoma of the prostate, one with Hodgkin's disease and 4 with myelogenous leukemia. All the patients with leukemia and Hodgkin's disease were receiving chemotherapeutic agents and had received blood transfusions. Normal or high PI (average, 135 μg/100 ml), low UIBC (average, 206 μg/100 ml) and normal or high transferrin saturation (aver-

age, 38.4%) characterized this group. Only the patient with carcinoma of the prostate had a low PI and tranferrin saturation.

The anemia in the small group of patients with *chronic infection and collagen diseases* was mild in all. Only one patient in each group showed depression of PI and a low siderophilin saturation.

The causes of anemia in patients with *cirrhosis of the liver* were frequently multiple. In 4 out of 7 the plasma iron was low but in only one was the UIBC slightly elevated, a patient with chronic blood loss. UIBC averaged 243 μg Fe/100 ml. All these patients exhibited marked hypoalbuminemia.

Although patients with acute *infectious hepatitis* were not anemic the results of PI and UIBC are interesting. Consistently these patients showed relatively high PI (average, 172 μg/100 ml) with normal or low UIBC (average, 234 μg Fe/100 ml) which resulted in the highest transferrin saturation (average, 44.9%) for any group.

The levels of PI and UIBC can change quite rapidly under the effect of specific treatment for anemia. This is illustrated in Figure 5, which describes these serially

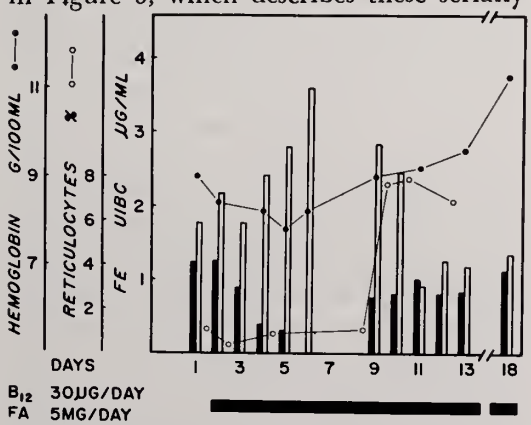


Fig. 5: Serial determinations of PI and UIBC in a case of tropical sprue.

in a case of tropical sprue treated with vitamin B_{12} and folic acid. A sharp drop in the PI concentration was evident by the second day of treatment. The UIBC rose reciprocally, reaching 360 ug/100 ml by the 6th day.

Discussion

The data presented here confirm in general the usefulness of PI and UIBC determinations in several clinical situations. The level of PI differentiates anemias into those characterized by normal or high values which includes megaloblastic and hyporegenerative anemias from those where this parameter is abnormally low. Within the latter group the determination of UIBC and the calculation of the degree of saturation of transferrin usually differentiates true iron deficiency anemia from other conditions where a low serum iron does not reflect depletion of total body iron stores but rather decreased iron transport due to various metabolic abnormalities.

Our results differ somewhat from those of others in some respects. The values for PI in normals tended to be lower than those reported by other using various methods (1,14). Ramsay (15) has also found that methods employing hot trichloroacetic acid for initial digestion as the one followed here tend to give low results. The wide normal range and the considerable day to day variation in individuals must be considered in the interpretation of single values for PI (1, 15). There was, however, little overlap between the values obtained in the healthy and the group with iron deficiency anemia.

The values obtained for UIBC are quite similar to those reported by others

using the same method (9, 11, 12, 13), but higher than usually found when colorimetric or spectrophotometric methods are used (12, 13). This difference is explainable in part by differences in the capacity of materials used to absorb iron in the different methods. The resin employed here will not remove iron attached to siderophilin while other absorbers such as magnesium carbonate do (11).

Because of the somewhat lower plasma iron values and the higher UIBC values our calculated % saturation of siderophilin in healthy subjects is lower than usually quoted in the literature (14). There was again, however, little overlap between normals and patients with iron deficiency.

As insinuated above, certain factors other than the body level of iron stores affect the levels of plasma iron and transferrin in the blood. *Depression of erythropoiesis* as is seen as a result of the effect of myelotoxic drugs will cause elevation of plasma iron and increased saturation of transferrin even before anemia makes its appearance (16). Other situations where there is *ineffective erythropoiesis* as in pernicious anemia, sprue, and di Guillielmo's disease, or where there is *hemolysis* associated with *block to the incorporation of iron* into the heme molecule as in poisoning with lead, *pyridoxine-responsive anemia* and *thallasemia* are also characterized by high plasma iron (1). *Increased mobilization* of iron stores as occurs in shock, acute bleeding, acute liver injury, will also produce sharp increase in plasma iron (17). In some cases, as in acute liver injury, the iron protein complex ferritin appears in the blood. The presence of this compound may explain the marked elevation of plasma iron which may occur in this condition without the complete saturation of transferrin which one might otherwise expect. Ferritin does not depend on transferrin for its transport in plasma (18).

The low level of iron in plasma during infection and chronic inflammation is apparently related to its *defective release* from tissue stores for transport by transferrin. Experimentally, transferrin-bound iron is utilized normally by the bone marrow in these cases (19).

Diseases characterized by *hypoalbuminemia,* be this due to impaired synthesis (liver disease), dietary deficiency or abnormal loss (renal disease, protein losing enteropathy) are characterized by low plasma concentrations of transferrin (4). This is related to the similarity of these proteins to albumin in their origin and disposition in the body.

Thus, in liver disease, where anemia of various etiologies is frequently a feature, determination of PI and UIBC can give useful clues as to what factors may be operative in a particular case. High PI and transferrin saturation may suggest hemochromatosis or acute hepatic injury; low PI and high UIBC point to blood loss, and normal or high iron in the presence of normal or low UIBC may indicate vitamin B_{12} or folic acid deficiency.

Blood transfusion and the parenteral administration of *iron complexes,* particularly when erythropoiesis is suppressed by metabolic abnormalities or *toxic chemicals* will result in high levels of PI and transferrin saturation. This is seen frequently during the treatment of leukemia and in some patients with anemia due to renal disease.

The case of tropical sprue described in Fig. 5 gives interesting clues as to the

physiopathology of the anemia in this disease. The initial findings of high PI and low UIBC are related to the ineffective erythropoiesis which characterizes untreated sprue. The rapid drop in PI which followed the initiation of B_{12}-FA therapy in this patient has been observed by others and attributed to rapid utilization of iron, mobilization of stores not keeping up (20). The fact that this sharp fall in plasma iron precedes the rise in reticulocyte count has suggested its use as an early index of response to specific treatment. The late drop in transferrin may be related to rapid protein utilization in hematopoiesis.

The determination of plasma iron, UIBC and % saturation of transferrin thus finds clinical application in the diagnosis of anemias the cause of which is not initially obvious. The method described here for UIBC is technically simple and appears to be reliable. It may be utilized wherever the basic facilities for the measurement of nuclear radiations are available. This test should be used in conjunction with others such as bone marrow examination, search for occult blood loss and examination of the blood smear, all being subject to interpretations in the light of the clinical situation.

Summary

Experience in the use of ^{59}Fe and an ion-exchange resin (IRA-400) incorporated in a polyether foam sponge for the determination of unsaturated iron binding capacity in the diagnosis of anemias is described. The normal range of values in males varied from 210 to 370 μg Fe/100 ml with an average value of 281. Patients with hypochromic anemia showed values from 323 up to 544 with an average of 410 μg Fe. Cases where the anemia was due to vitamin B_{12} or folic acid deficiency, renal desease, cancer, collagen diseases, chronic infections or liver cirrhosis showed a wide range of values usually in the normal range or below.

The method was found to be technically simple and apparently reliable. Our results are similar to those of others confirming the fact that results for latent iron binding capacity tend to be higher than when colorimetric methods are used.

The determination of unsatured iron binding capacity and percentage saturation of siderophilin is particularly useful in the diagnosis of iron deficiency anemia and its differentiation from other types where the plasma iron may also be low (infection, collagen disease, cancer) but unsaturation of iron binding protein is not increased.

Resumen

Se resume una experiencia en el uso de ^{59}Fe y una resina de intercambio iónico, tipo IRA-400, incorporada en una esponja de poliéteres en la determinación de niveles de siderofilina. En un grupo de varones saludables se obtuvieron niveles entre 210 y 370 μg Fe/100 ml con un promedio de 281. En los casos de anemia ferropénica, los valores variaron entre 323 y 544 y el promedio fue de 410 μg Fe. En los casos con anemias megaloblásticas, enfermedad renal, cáncer, enfermedad del colágeno, infección crónica o cirrosis del hígado, se encontró una amplia gama de valores, predominantemente dentro de los límites normales o bajos.

El método descrito es sencillo y aparentemente confiable. Nuestros resultados son

similares a los de otros investigadores y confirman el hecho de que tienden a ser más altos que cuando se usan métodos colorimétricos.

La determinación del grado de saturación de siderofilina es de valor en el diagnóstico de anemia por deficiencia de hierro y su diferenciación de otras anemias en que el hierro plasmático es bajo pero la saturación de siderofilina no está disminuída.

Acknowledgment

We thank Dr. R. Menéndez-Corrada for review of the manuscript, Dr. Paul F. Crosby for statistical advice, and Mr. Vicente Besares and Mrs. Brunilda González for technical assistance.

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REHABILITATION OF CHRONIC PULMONARY OBSTRUCTIVE DISEASE

Herman J. Flax MD, FACP

Breathing in the normal person is an automatic process controlled by the elasticity of healthy lung tissues. Muscles assist breathing by stretching the chest cavity on inspiration, permitting the lung to expand, and by relaxing on expiration squeeze the chest cavity forcing the air out. The patient with chronic pulmonary obstructive disease has lost the elastic recoil property of the air sacs and cannot force the used air out of the lungs.

The combination of normal elastic lung tissue and muscular contracture of the chest wall maintains a negative pressure during both inhalation and expiration, greater on inhalation. When elasticity is lost as a result of chronic obstructive pulmonary disease, a positive pressure develops. The patient cannot eliminate the CO_2 present in the alveoli and especially the pulmonary dead space, causing a rise in arterial partial pressure of CO_2.

This produces a state of chronic oxygen debt, which is not relieved very much with tremendous voluntary efforts of respiration (1). The increased amount of work in breathing and the small amount of oxygen gained through this exertion is not rewarding enough. Also, the slightest strain, physical or emotional, or any change in ventilation-perfusion surface will be manifested by immediate dyspnea.

These patients will not show any respiratory response to inhalation of high CO_2 mixtures, because they cannot remove the CO_2 already produced in their respiratory tree and free themselves from O_2 debt even with the most strenuous voluntary effort. They are broken in body and in spirit, and they hang around without hope of ever being able to return to a productive life or pleasurable retirement.

Breathing exercises and other physical therapeutic measures, such as postural drainage (2) for those with a great amount of thin, non-viscid sputum, tapping the chest wall to dislodge thick, sticky sputum combined with postural drainage, other vibrocompression devices (3) blow-bottle exercises, and the spring-balanced Gordon-Barach emphysema belt (4) can be considered only as supplements to positive-pressure therapy. Suffice it to say that an intermittent positive-pressure breathing valve combined with aerosol bronchodilators and oxygen therapy is the most rapid way to obtain relief from dyspnea and is the most important therapeutic measure. Exercises

Presented at Annual Meeting of the Puerto Rico Medical Association, 11-17-67.

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teach the patient to improve the rate, depth and character of respiration by strengthening weakened respiratory muscle and improving their functional efficiency.

At times, a portable oxygen tank is a valuable asset to use in a training program to increase the exercise tolerance of these patients (5). This is especially valuable for the patient with incapacitating dyspnea due to pulmonary emphysema. Millet et al (6) showed that training the pulmonary cripple in exercise using 40% oxygen inhalation promoted a state of well-being and made possible a greater physical independence. These patients showed an increase in work tolerance, and oxygen permitted training where, otherwise, it would have been impossible. Oxygen inhalation lessened physiologic stress by reducing the respiratory drive and making a slower and more efficient respiratory pattern feasible.

As yet the cause of this disease remains a mystery. It is, perhaps, for this reason that therapy has been not too successful in the past. However, when we realize that emphysema and chronic bronchitis constitute one of the leading causes of death in the United States of America, almost of epidemic proportion, and emphysema alone incapacitates one out of every 14 wage earners and is second only to heart disease as a crippler according to Social Security Administration records (7), it is small wonder that the Health, Education and Welfare Chronic Respiratory Disease Program is attacking this problem by supporting diagnostic clinics, intensive care demonstration units and emphysema prevention projects throughout the nation. These rehabilitation projects restore 50% of the severely disabled pulmonary cripples to self sufficiency and in many cases to employability by means of a program of breathing exercises, postural drainage, physical conditioning, drug and inhalation therapy, and regular check-ups.

Several investigators, Miller in Dallas (8), (9), Sheldon in San Francisco (10), Beck in New York (3), (11), and Sinclair in London (12) have emphasized the pertinent principles and precepts of Barach (4) and have written extensively on breathing exercises and other rehabilitation measures in the treatment of patients with chronic obstructive lung disease. Dorinson (13) summarized the problem nicely and suggested some recommended breathing exercises, which is basically the program used at the Dr. E. Fernández García Pulmonary Disease Hospital.

The patient it taught to empty his airway by forced exhalation. This is contrary to the patient's desire to get more air into the lungs. The secret of success in promoting breathing exercises is to convince the patient not to struggle to inhale, but to keep calm and deflate the lung by exhaling; whereupon, inhalation becomes easy. It is necessary, therefore, to teach the patient good diaphragmatic control. Barach (4) discusses methods to strengthen and control of the diaphragm. We try to have the patients avoid thoracic-cage expansion by compressing the lower-rib cage with their own hands and strengthen the abdominal and diaphragmatic muscles by placing a sand bag on the abdomen or have the physical therapist offer resistance to breathing by compressing the chest cage manually.

Relaxation technics, general conditioning, and shoulder-girdle mobilization exercises are used routinely in all patients. Thorough patient education in the na-

ture of his disease is given my members of the staff, group therapy discussions of medical problems are held routinely. It is heartening to see some of the patients teaching others the fundamental technics of breathing exercises under the supervision of the physical therapist. Although individual instruction and reassurance is necessary at the beginning, almost all of the patients, regardless of age, learn the entire program of exercises very quickly. It is extremely important that the exercises be kept simple, and new exercises are added a few at a time. Once the patients lose their fear of producing dyspnea by the added exertion and increased pulmonary work, they enjoy and look forward to the sessions.

Unfortunately, the majority of our patients start their program of rehabilitation measures late in the course of their disease. Also, many of the older patients fail to practice their exercises once they are discharged from the hospital. Old and young must be motivated constantly to improve their respiration, and a daily regime outlined for daily practice throughout life.

It is not too far-fetched to consider the organization of day clinics for the pulmonary cripple much in the same fashion as for the care of the psychiatric outpatient. Here, he can come daily to fraternize with fellow sufferers, work in a hobby shop or attend vocational training in a sheltered workshop, receive intermittent positive-pressure breathing assistance with oxygen and aerosol bronchodilators, clear his airways by cough, postural drainage and percussing the chest wall, verbalize his fears, frustrations and socio-economic problems, do his breathing exercises, as well as get general medical care. Each severely obstructive pulmonary disease patient should be given a prescription for a portable oxygen cylinder connected to a catheter for emergency inhalation just as the paraplegic receives a wheel chair, the hemiplegic a drop-foot brace, or the amputee a prosthesis to improve their functional abilities.

In summary, breathing exercises are but one part of the total rehabilitation program for the obstructive air-way patient. Copies of the exercises are given to the patients, and this treatment is supervised by the Physical Medicine and Rehabilitation Service. This therapy should be a part of the patient's daily regime for as long as he lives. Our purpose, as was so eloquently stated by Dr. George Morris Piersol many years ago, "is not only to add years to life but to add life to years".

Resumen

Los ejercicios de respiración solamente son parte del programa de rehabilitación total del paciente con obstrucción de las vías respiratorias. Copias de los ejercicios de respiración son entregadas a los pacientes y ese tratamiento es supervisado por el Servicio de Medicina Física y Rehabilitación. Además de los ejercicios de respiración a cada paciente enfisematoso se le debe entregar una receta para un cilindro portátil que suministra oxígeno conectado a una sonda para inhalación de emergencia. Sería posible pensar en la organización de clínicas diurnas para los pacientes con enfermedades de obstrucción pulmonar crónica. En este sitio, el paciente puede venir todos los días para fraternizar con los compañeros con enfermedad similar, asistir a los talleres de recreación,

tomar un curso de adiestramiento vocacional en un taller bajo techo, recibir asistencia para respirar con un equipo de presión positiva intermitente utilizando oxígeno y broncodilatores con earosol, limpiar la vía respiratoria tosiendo con drenaje postural y con percusión en la caja torácica, exteriorizar sus miedos, frustraciones y problemas socio-económicos y hacer sus ejercicios de respiración además de recibir cuidado médico general. Este tratamiento sería parte del régimen diario del paciente para toda la vida. Nuestro propósito es como dijo tan elocuentemente hace años el venerable maestro, George Morris Piersol, "No es solamente añadir años a la vida, sino vida a los años".

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CASE REPORT

CAROTID BODY TUMORS

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The rarity of carotid body tumors in Puerto Rico and throughout the world (1) has prompted us to report a case we recently operated on, and to review the current knowledge and management of carotid body tumors.

Case Report

The patient, a 49-year-old white veteran, was found to have a non-tender 2 x 3 cm mass in the right side of the neck while stationed at Munich, Germany in May 1960. No work-up was made at that time. One year later he was again seen in the same dispensary and a swelling of the right parotid region was noted. This was said to have been present for five or six years with no appreciable change in size. The examiner noted "No discrete tumor palpable in the parotid", however, "there appears to be an enlarged 3 x 4.5 cm lymph node on the right upper neck". On May 3, 1961, a sialogram revealed an "enlarged right parotid gland". The next day a subtotal parotidectomy was performed. A review of the operative report reveals that "at no time was a definite tumor mass felt in the parotid, however, in its central portion there appeared to be some thickening and fibrosis". Microscopically the sections of salivary gland examined "showed no evidence of tumor, the overall histologic findings are those of a mild, widespread, but rather patchy form of chronic sialadenitis". The patient states that the day after the operation the same mass was still present in the right neck as before and it has remained asymptomatic and without change until the present.

In October 1963, he was admitted for the first time to the hospital, for a gastrointestinal evaluation (he is receiving compensation because of chronic duodenal ulcer disease) and at that time "an induration in the right parotid region with overlying scar" was described.

At the present admission a 2 x 4 cm, nontender, firm, slightly lobulated mass was found in the right side of neck below the angle of the jaw. The mass was freely movable in the lateral plane of the neck. No thrill was palpable. The mass was located beneath a well-healed surgical scar. (Figures 1, 2)

A preoperative diagnosis of recurrent mixed tumor o fthe parotid gland was made and the patient was operated upon. A very vascular pinkish mass was found at the bifurcation of the common carotid artery. It measured 4.5 x 2 cm and it completely displaced the structures about the carotid bifurcation. It was necessary to perform a carotid arteriogram in order to identify with certainty the internal carotid artery prior to excision of the mass. The mass was removed by blunt and sharp dissection along the subadventitial plane of the arteries. This was accomplished without interrupting the internal carotid circulation. The right vagus nerve was within this vascular mass so that it was necessary to remove it along with the mass. The patient's postoperative course was uneventful except for right vocal cord palsy.

Microscopic section revealed the characteristic picture of carotid body tumors of rests of epithelioid cells (Zellballen) enveloped by a fibrovascular stroma (Figure 3).

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Presented at the Semi-Annual Convention of the Puerto Rico Medical Association on August 11, 1967.



Fig. 1: Anterior view of the patient.



Fig. 2: Lateral view of the patient.

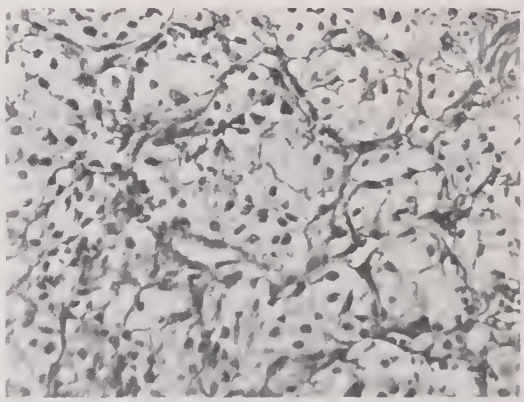


Fig. 3: Photomicrograph of the patient's tumor showing the characteristic Zellballen architecture of carotid body tumors. (H & E, X 450).

Comment

Probably this tumor was present at the first operation and was thought to be regional lymphadenitis secondary to sialadenitis. We were mislead by the history into thinking that we were dealing with a persistent mixed tumor of the parotid gland. It was not until the tumor was exposed that we realized we were dealing with a carotid body tumor. This case demonstrates the remarkably slow rate of growth of these tumors and the paucity of symptoms associated with them.

Discussion

Carotid body tumors are rare but must be considered in the differential diagnosis of masses in the lateral aspect of the neck. They are the most common (1) of the group of tumors histologically similar and classified as chemodectomas. Microscopically chemodectomas show a characteristic Zellballen architecture consisting of nests of epithelial cells surrounded by highly vascular stroma (2). Chemodecto-

ma have been reported to originate in the carotid body, the glomus jugulare, the vagus nerve at the level of the ganglion nodosum and its auricular branch, the tympanic ganglia of the glossopharyngeal nerve, the ciliary ganglia, the aortic bodies in the mediastinum, the femoral canal, eye, mandible, ileal mesentery, and hypoglossal nerve (1). Their name and clinical manifestations vary according to site of origin.

The carotid bodies are situated bilaterally at the bifurcation of the common carotid artery, lying between its external and internal branches. As Boyd has emphasized (3) they are located within the adventitia of the carotid vessels, this being the basis for the current subadventitial surgical approach to these tumors. The carotid bodies are chemoreceptors, being sensitive to decreased levels of oxygen and increased levels of carbon dioxide and of hydrogen ion concentration in the blood. Reflexly they produce changes in rate and depth of respiration and an increase in blood pressure and vasoconstriction without change in heart rate. These changes are thought to be mediated through the central nucleus of the glossopharyngeal and vagus nerves. There is no clinical evidence that the carotid bodies secrete epinephrine or any other hormone-like substance.

Carotid body tumors occur as a pinkish tan mass of tissue located on the posterior aspect of the common carotid artery bifurcation. They are extremely vascular and usually well encapsulated. Le Compte (2) has classified them histologically into three types. The first type has the normal microscopic pattern of the carotid body. The second type has an adenoma-like appearance in which the cells resemble epithelium with scanty stroma. The third type has an angioma-like appearance with the chief cells showing spindle or crescent shapes. These three histologic patterns apparently have no bearing on the behavior of the tumor. Presently there exists considerable controversy as to the benign or malignant nature of these tumors. Thus the reported incidence of malignancy varies widely in different series. It has been reported as high as 50% (4), whereas other authors, as Le Compte, doubt if any become truly malignant (2). Reese et al (5) after reviewing the reported series concluded that the incidence of malignancy is probably about 10%. However, even if the microscopic picture is benign, these tumors can involve vital structures because of their location. If untreated they grow slowly and may cause death of the patient by local invasion, compression of vital organs, difficulty with respiration and swallowing, vascular occlusion, or occasionally hemorrhage (6). Thus they may be considered clinically "malignant" even though distant metastases rarely occur.

Carotid body tumors usually present as an asymptomatic mass of long duration in the lateral aspect of the neck, 2 to 5 cm in diameter when first seen by the physician. Occasionally they may produce symptoms by involving the nearby structures causing tenderness, dysphagia, carotid sinus syndrome, pain in the neck or ear, hoarseness and headache (8). The mass is freely movable laterally but not up or down, which differentiates these tumors from other cervical masses in this region (branchiogenic cysts, aneurysms, metastatic lesions from the thyroid, lymphomas, and neurofibromas). A bruit may be heard over the mass. Occasionally caro-

tid body tumors are bilateral (9, 10). They have been reported to have a familial tendency (11, 12).

Carotid angiography is the most important diagnostic aid. It outlines the internal and external carotid artery, spread apart by a vascular mass in a "lyre-like" configuration (6). Angiography is also helpful in planning the operation, in assessing the patency of the vessels and degree of collateral circulation. Because of the rare occurrence of bilateral tumors both carotids should be visualized (6). Angiography is performed by retrograde brachial catheterization in order to avoid hemorrhage caused by the needle inadventently entering the highly vascular lesion (6).

The natural history of both benign and malignant carotid body tumors is one of slow growth over a period of years. Because of this, and because of the former high incidence of surgical complications and mortality from interruption of the internal carotid artery, many surgeons felt that surgical intervention was only warranted in exceptional cases. Recently, improved diagnostic methods and new surgical techniques have lowered the morbidity and mortality, and together with the increasing awareness of the potential malignancy of these tumors, have given rise to a more aggressive management (13). Since Gordon-Taylor described the subadventitial approach the majority of carotid body tumors are now excised successfully by this method without interruption of the circulation. If it becomes necessary to excise the internal carotid artery with the tumor, one measures the pressure in the internal carotid artery after proximal carotid compression. A fall of 50 to 60% (14, 15) in intra-arterial pressure distally indicates that permanent interruption of carotid flow would lead to cerebral ischemia and death. Flow is reestablished by arterial prosthesis, vein graft, or by transecting the external carotid artery and anastomosing its proximal end to the distal end of the transected internal carotid artery in an end-to-end fashion. Thus the importance of preoperative evaluation of the patency of the arteries and extendt of collateral circulation by angiography.

Although an occasional tumor will show some response to radiation therapy, results of this therapy have generally been disappointing (6). It seems logical to reserve its use to cases where the tumors are inoperable and symptomatic.

Summary

A case report of a patient with a carotid body tumor is presented. The current knowledge and management of carotid body tumors is discussed. We believe these tumors should be excised surgically whenever diagnosed.

Resumen

Se presentó el caso de un paciente con tumor del cuerpo cartotídeo. El conocimiento actual y el manejo de estos tumores fue discutido. Es nuestra opinión que estos tumores se deben remover quirúrgicamente cuando se diagnostican.

Acknowledgement

Dr. G. Ramírez de Arellano, Asst. Chief, Laboratory Service, was responsible for the interpretation of the histological material.

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CLINICO PATHOLOGICAL CONFERENCE

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Laszlo Ehrlich, MD

Clinical Abstract

A 79 year old colored male admitted for the first time on September 20, 1966 with 1½ months history of post-prandial fullness, mild epigastric pain, nausea and vomiting. He had lost 20 lbs. in one year.

The patient's past medical history was unremarkable except for cataract operations in 1962. He smoked 3 packs of cigarettes per day for the past 59 years and drank alcohol to excess up to 5 years prior to admission.

Physical examination revealed a well developed, undernourished colored male in no distress. Blood pressure, 120/80 mm Hg., pulse, 82/minute, temperature, 98°F. weight, 113 lbs. There was complete [illegible] dentia with normal tongue and mucosa. The eyes showed evidence of corneal scars from previous bilateral cataract extraction. These was no cervical, supraclavicular, nor axillary lymphadenopathy. The heart and lungs were normal. The abdomen was soft and depressible. There was mild tenderness at the epigastric area without guarding nor rebound tenderness. A 3 × 4 cm hard, smooth, fixed mass was palpable to the right of the midline at the epigastric area.

The hemoglobin was 8.8 g %; hematocrit, 34%; WBC, 13,650; 66% neutrophiles, 7% bands, 24% lymphocytes, 3% eosinophiles. Urinalysis was normal. VDRL microflocculation was non-reactive. Stools were negative for ova and parasites. Serum bilirubin was 0.3 mg %. Prothrombin time was 13.8 seconds (control, 14 seconds). Serum sodium was 138 mEq/L; CO_2, 21 mEq/L; chlorides, 96 mEq/L; potassium, 4.9 mEq/L. Alkaline phosphatase was 9.8 SJR units. Blood urea nitrogen was 15.3 g %; glucose, 53 mg % (Somogyi). Total protein, 6.3 g %; 3.1 g % albumin; 3.2 g % globulin. Bromsulphthalein retention was 2% in 45 minutes.

Electrocardiogram revealed non-specific ST and T wave changes. Roentgenogram of the chest was essentially negative. An upper gastrointestinal study done at another institution was interpreted as carcinoma of the gastric antrum.

The patient received a transfusion of 500 ml of whole blood and on September 27 underwent an exploratory laparotomy which revealed a tumor at the lesser curvature of the stomach in the region of the antrum about 4 × 5 cm in size. An 85% subtotal gastrectomy, 40% subtotal pancreatectomy, omentectomy, splenectomy and antecolic gastrojejunostomy was performed. Histologic diagnosis was medullary carcinoma, fungating and superficially ulcerated, extending to the serous coat and not infiltrating the pylorus nor the duodenum. Fifteen lymph nodes were negative for metastases

Presented at the Annual Meeting of the Puerto Rico Medical Association, San Juan, Puerto Rico, November 17, 1967.

Post operative course was complicated by bilateral basal pneumonitis, which responded to antibiotic therapy. He was discharged on October 16, 1966.

The patient was readmitted asymptomatic, on November 2, 1966 for a course of chemotherapy consisting of 5 fluoro-21-deoxyuridine, total dose of 12,810 mg. Upon discharge on November 25 his hemoglobin was 10 g %; hematocrit, 33%; WBC, 4,986; 51% neutrophiles; 5% bands; 39% lymphocytes; 2% eosinophiles; platelet [illegible]/mm³. Therapy was well tolerated. Blood urea nitrogen and urinalynis were normal.

Final admission was on March 14, 1967 because of generalized edema, marked weakness and "aching joints" of one month duration. He denied urinary frequency, dysuria, hematuria, fever or chills. There was easy fatigability but no shortness of breath, cough, expectoration, chest pain or paroxysmal nocturnal dyspnea.

Physical examination revealed blood pressure of 180/115 mm Hg; pulse, 88/min.; temperature, 97.8°F; weight, 137 lbs. Conjuctivae were pale. No jugular vein engorgement. The heart and lungs were normal. Neither the spleen, liver or kidneys were palpable. There was moderate edema of the anterior abdominal and chest wall. Neurological examination was normal. Rectal examination, negative. The hemoglobin was 12.2 g %; hematocrit, 37%; WBC, 11,557; 57% neutrophiles; 39% lymphocytes; 2% monocytes; 1% eosinophiles; 1 basophil; platelets, 198,000/mm³. Urinalysis: specific gravity of 1.010, 4+ albumin, negative for sugar, 20-25 RBC/HPF, 40-50 WBC/HPF. Corrected sedimentation rate, 8 mm/hr.; blood urea nitrogen was 16.5 mg %; blood sugar, 70 mg %; total protein, 4.85 g %; albumin, 1.7 g %; globulin, 3.15 g %; serum uric acid, 9.15 mg %; cholesterol, 260 mg %; serum Na, 146 mEq/L; potassium, 3.9 mEq/L; chlorides, 107 mEq/L; CO_2, 19.4 mEq/L; alkaline phosphatase, 7.4 mg %; bromsulphthalein retention, 27.5% in 45 minutes. Serum protein electrophoresis: albumin, 47.52%; $alpha_1$, 4.95%; $alpha_2$, 13.37%; beta, 15.84%; gamma, 18.32%. Serum iron was 93 μg Fe/100 ml with an unsaturated iron binding capacity of 232 μg Fe/100ml. Urine for albumin was 6.16 g in a volume of 1,100 ml in 24 hours and was positive for doubly-refractile bodies.

An electrocardiogram on March 16, 1967 was interpreted as having left axis deviation with anterolateral myocardial ischemia.

Roentgenogram of the chest on March 16, 1967 showed a left pleural effusion with a small triangular density. Flat plate of abdomen was obscured by gas-dilated bowel completely obliterating the kidney shadows. Upper gastrointestinal study showed subtotal gastrectomy with well functioning stoma.

The patient was transferred to the Medical Service on March 27, 1967 where he was started on diuretics (hydrochlorothiazide 50 mg, spironolactone 100 mg daily and furosemide 120 mg daily). There was approximately 18 lbs. weight loss in four weeks, the weight remaining around 120-117 lbs. in the latter part of April and the beginning of May. The blood pressure persisted around 200 systolic and 110 diastolic with a urinary output of over 1000 ml/24 hrs.

On May 8 he was started on prednisone 15 mg q.i.d. orally. There was further

loss of weight to 102 lbs. On May 22 the patient started complaining of constant upper abdominal pain particularly at the right upper quadrant. There was no nausea or diarrhea. Examination revealed tenderness over the right upper quadrant without distention, the area of liver dullness appeared to be decreased. A hemoglobin determination was 11.2 g %; hematocrit, 38%; WBC, 23,441 with 80% neutrophiles, 10% bands, 6% lymphocytes, 2% monocytes, 2% eosinophiles. A serum amylase was 90 modified somogyi units. Alkaline phosphatase was 8.2 SJR units. Roentgenograms of the abdomen erect and recumbent were "grossly negative". Chest X-ray revealed that the previous pleural reaction had almost completely cleared. Prednisone was discontinued and following a day of antibiotics the pain decreased in intensity and the temperature remained around 100°F. On May 28 the right upper quadrant pain increased in intensity with radiation to the right shoulder and increasing with respiration. There was tenderness and rebound in the right upper quadrant of the abdomen with tenderness over the right flank and lower ribs. The right diaphragm was elevated. There was decrease of breath sounds and dullness at the right lower lobe. Chest X-ray on May 28, 1967 was interpreted as infrapulmonary effusion, left chest. X-ray of abdomen showed moderate gaseous dilatation of the bowel without fluid levels, suggestion of a mass in the right upper quadrant associated with some mottling and an opacity in the left abdomen near L4. That same day an exploratory laparotomy was performed. Post-operatively he was given hydrocortisone 100 mg every six hours, chloramphenicol 1 g every 8 hours, procaine penicillin 800,000 units every 12 hours. On the third post operative day the blood pressure dropped to 110 systolic, 70 diastolic, the temperature was 95.6°F with a pulse of 90/min. with adequate urine output. Additional doses of hydrocortisone and blood transfusion of 500 ml were given. The following day, June 2, 1967, the blood pressure was unobtainable and he expired.

Clinical Discussion

*Dr. Hyman J. Zimmerman**

We have for discussion this morning an elderly male whose clinical odyssey covered a period of approximately one year and consisted of three quite distinct phases. The first was that of a rather obvious gastric carcinoma, the second was one of a dramatic and interesting renal complication and the third, which delivered the coup-de-grace, was an abdominal catastrophe and just prior to that, some pulmonary complications.

The first phase, then, was that of a man who came in with post-prandial fullness, epigastric pain, nausea and vomiting, wasting and an easily palpable mass. There was little doubt, I am sure, in the examiner's mind, that he was dealing with a gastric carcinoma which was then properly confirmed by X-ray, demonstrated at laparotomy and resected. The laboratory data at that time showed the anemia that could have been expected. There was slight eosinophilia. Even though it was described as only 3%, it was 3% of almost 14,000 cells. When one sees leukocytosis one expects eosinopenia. Accordingly, the slight eosinophilia was worth noting although

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I did not know quite what way to make of it. It was also worth noting that liver function tests revealed normal values. The alkaline phosphatase value was meagerly elevated at 9+ units.

One might have to assume at that time that there were either no metastasis to the liver or that there were few, since 90% patients with metastatic involvement of the liver have an abnormal BSP excretion, and over 80% have abnormal alkaline phosphatase levels, while normal values do not exclude metastasis, they do offer some reassurance. Apparently the surgeon found no evidence of metastasis in the liver or in the regional lymph nodes. At operation it was found necessary to remove the spleen, half of the pancreas, some neighboring lymph nodes and, of course, 85% of the stomach, which included all the carcinoma that could be seen.

Phase one, then, was essentially over. Thereafter his course was uneventful for a number of months, punctuated only by the fact that, two months after operation, it was chosen to give him a course of chemotherapy with the riboside derivative of 5-fluorouracil. He was given a full course, again without event, except for a very mild neutropenia in which the white count dropped to a little over 4,000.

Approximately four months later he returned to the hospital, having apparently felt fairly well until a month before reporting. At that time he had developed a new set of complaints. He had edema, weakness and arthralgia. It was quite clear that the marked edema observed on entry was not due to heart failure, since his neck veins were not distended. And you will note that the presence in the urine of doubly refractile droplets was described. This refers to the droplets that are seen in fatty casts and oval bodies. These lipid laden desquamated renal epithelial cells are virtually diagnostic of the nephrotic syndrome. They are found when there is massive proteinuria. Accordingly before any other laboratory data had been returned one could have made a diagnosis of edema secondary to the nephrotic syndrome.

The elements of the nephrotic syndrome which, of course, you all know, are edema secondary to hypoalbuminemia which in turn is the result of massive proteinuria and is almost always accompanied by the oval fat bodies previously mentioned. Our patient had all of these features, lacking only hypercholesterolemia, for the complete nephrotic syndrome, —an important point that I will come back to later. He had a serum albumin of 1.7 g %; daily urinary protein loss of 6 grams per day; there was marked edema; and the urine contained oval fat bodies.

One might then make a departure for a moment, and consider the possible cause of this nephrotic syndrome and its presumed relationship to the underlying disease.

Despite the very large number of causes of the nephrotic syndrome, there are some helpful features that permit distinction between those causes of nephrotic syndrome that are not be entertained here, and those causes that are relevant to the present circumstances. It is quite apparent that a man who had a normal urine 6 months and 4 months prior to this nephrotic edema, does not have chronic glomerulonephritis accountable for the clinical picture. It would be extremely unusual for a membranous nephritis to make its appearance in a 79-year old man although it is con-

ceivable. He was not diabetic and may be presumed not to have diabetic glomerulosclerosis; it would be flattery for him I am sure to consider that he might have secondary syphilis. Quartan malaria does not occur in this area, and sickle-cell anemia would have long since had been recognized in the patient. While systemic lupus or polyarteritis nodosa need to be considered in these circumstances, there was no other evidence for these. It would be unusual for lupus to appear in this age group, although certainly not for polyarteritis nodosa. Nevertheless, I would like to consider later the possibility that a collagen-like syndrome secondary to carcinomatosis might have produced the nephrotic syndrome here. Certainly a very important cause to consider in a patient who had no previous evidence of renal disease and then presents with a full blown abruptly developed nephrotic syndrome, is renal vein thrombosis. As you know, bilateral renal vein thrombosis and even at times unilateral renal vein thrombosis can lead to full blown nephrotic syndrome. This is a difficult diagnosis to recognize or to establish in a patient who hasn't had any trauma and who has not had any back or flank pain. The cardinal features of renal vein thrombosis are back or flank pain, marked proteinuria and edema, thromboembolic episodes and marked hematuria. This man had neither trauma nor the pain; he certainly had the proteinuria and edema. He had, as I may now move on to comment briefly, some evidence of thromboembolic disease. Shortly after presenting with the nephrotic syndrome, he was found to have a left hydrothorax and radiographic abnormalities of the lung were noted, as you will see in a little while, that were quite consistent with pulmonary infarction.

It is worth recalling that surveys of patients with carcinomatosis have revealed a 1% incidence of asymptomatic renal vein thrombosis, that is asymptomatic on its onset although it may be lead to a nephrotic syndrome.

As you know, a number of chemical agents have been found to lead to the nephrotic syndrome in humans. These have included anticonvulsant drugs, probenecid, penicillamine, etc. We also know that allergic reactions, severe reactions to poison oak and poison ivy, have lead to the nephrotic syndrome with a polyarteritis nodosa-like histologic reaction. This category must be considered when the nephrotic syndrome develops fairly acutely. Our patient was exposed to none of the known agents that have led to the nephrotic syndrome. I was unable to find any reports of nephrotic syndrome having been produced by the chemotherapeutic agent used in this patient, and I would choose to dismiss that likelihood. Without evidence for any hyperergic response to any agent to which this patient was exposed, again one can hardly invoke an allergic type of nephrotic syndrome.

Finally we must consider renal amyloidosis as a cause of this patient's nephrotic syndrome. Most other causes of nephrotic syndrome leave hepatic function normal. When one sees a patient with nephrotic syndrome and distinctively impaired liver function as in this case, one should consider strongly the possibility of amyloidosis of the kidney and liver. And this indeed seems relevant here. Of course, a patient who had a gastric carcinoma resected 4 or 5 months earlier, and who comes

in with BSP retention of 27% may now have hepatic metastases. I think that is rather unlikely. It is unlikely because we are told by the physical examiner in the record that the liver was not significantly enlarged, and certainly metastatic carcinomatosis of the liver able to account for a 27% BSP retention should lead to readily demonstrable hepatomegaly. Nevertheless, the possibilities remain of either atypical metastatic disease or amyloidosis accounting for the abnormal liver function. The alkaline phosphatase which remained normal is somewhat paradoxical for both hepatic amyloidosis and metastatic disease since either if leading to BSP retention of this degree, would be expected to lead to hyperphosphatasemia as well.

Amyloidosis has been found as a complication of carcinomatosis in 0.5 to 1% of instances at autopsy. Whereas in the past the most important causes of secondary amyloidosis were forms of chronic suppurative disease, in recent years neoplastic states and rheumatoid arthritis have become more important underlying diseases. Indeed carcinoma and lymphoma probably constitute the single biggest group of causes. The carcinoma most often associated with amyloidosis is renal carcinoma; others have been noted, and certainly gastric carcinoma could have been the forerunner of amyloidosis.

I would like to now comment briefly on the collagen-like syndrome that may be observed in patients with carcinomatosis. As you are all aware, some 20% of patients with dermatomyositis have an underlying carcinoma responsible. Occasionally the dermatomyositis may be associated with other changes in other tissues that are quite consistent with collagen disease and occasionally renal changes occur that resemble those of polyarteritis nodosa. Accordingly, it is conceivable, although not likely, that the nephrotic syndrome in this patient might have been related to a collagen-like response to his underlying carcinomatosis. In most instances the nephrotic syndrome is accompanied by hypercholesterolemia. Only when wasting is extreme does one fail to see hypercholesterolemia. Wasting could complicate any of the causes of nephrotic syndrome in a patient with carcinomatosis and account for the absence of an elevated cholesterol level. However, the cause of nephrotic syndrome which is most commonly associated with a normal cholesterol level is renal amyloidosis. Accordingly we would suggest that the normocholesterolemia would be most consistent with the nephrotic syndrome having been due to renal amyloidosis.

I would like to make a case for dermatomyositis out of the weakness of which this patient complains but it is a very feeble case, feeble because we are told only that he complained of severe weakness. We aren't told whether it involved any special muscle group, or whether he was just debilitated and exhausted. Furthermore, we are not given serum transaminase values. If the transaminase values had been elevated in this patient, it would have been consistent with the diagnosis of dermatomyositis secondary to carcinomatosis. Conceivably, though rarely, nephrotic syndrome might be attributed to renal involvement in dermatomyositis, but it is an excessively rare phenomenon. In this connection, the development of hypertension was of interest.

The patient had a blood pressure of

120/80 when he was seen for the first time. When he came back to the hospital the diastolic pressure was 110 mm or above. While this might reflect a collagen-disease-like syndrome, it might also reflect an amyloidosis-induced renal lesion.

The patient was treated for his edema with diuretics, and showed some measure of improvement. However, after a month of this treatment, without adequate response to therapy, he was started on moderately large doses of corticosteroids. He received prednisone, in doses of 60 mg a day, and apparently had either some improvement of edema or loss of tissue since he lost weight. About two weeks after being started on steroids, another group of troubles began, which we have chosen to call phase 3 of this illness.

He developed pain and tenderness of the right upper quadrant of the abdomen with radiation of pain to the shoulder. He had a remarkable leukocytosis, but at this time still had a normal alkaline phosphatase level. X-ray examination at this time showed and elevated right diaphragm. We are told about a mass that, after exploration, the results of which aren't told as aparently they reveal the answer, he developed an episode of terminal collapse and died. This might be a good time to see the X-rays, please.

*Dr. Laszlo Ehrlich**

This is a polygraphic study (Fig. 1) of the G.I. examination done outside on September 12. The film was referred to us with the diagnosis of carcinoma of the gastric antrum. The lesion is obvious, exhibiting a narrowed and rigid antrum.

This chest film (Fig. 2) of March 16

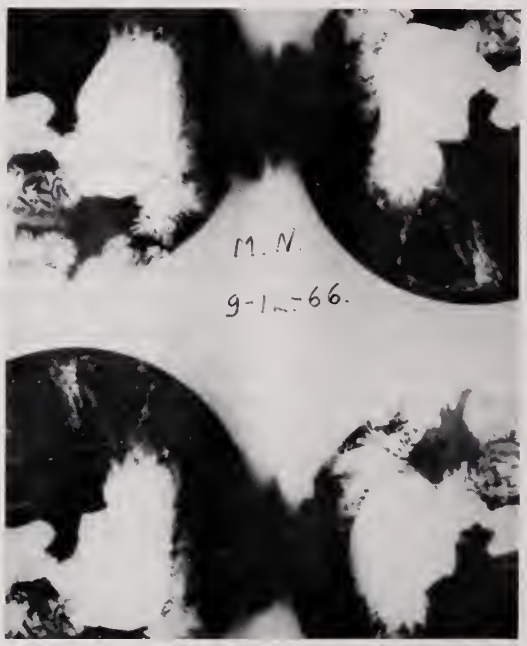


Fig. 1: Polygraphic study of GI examination Sept. 12.

shows the left lower lung field to be obscured by a diffuse density which we interpreted as pleural effusion; a triangular opacity in the same area may represent a small loculation or a subsegmental atelectasis or perhaps a small infarct. The chest film of May 23 shows almost complete clearing of the pleural reaction at the left base.

This chest film (Fig. 3) taken 5 days later, May 28, shows what appears to be an elevated left hemidiaphragm; its contour is ill-defined. This feature calls for a special examination which consists of placing the patient in the left lateral decubitus position and take a film with horizontal beam.

This is the special view (Fig. 4) which reveals that the left diaphragm is not elevated, and that the density that imitated

* *Chief, Radiology Service.*



Fig. 2: Chest roentgenogram on March 16 showing left pleural effusion.



Fig. 3: Chest roentgenogram on May 28 suggesting elevation of the left diaphragm.

it in the previous chest film now is running along the left chest wall. This means that we are dealing with a special pleural effusion called "infrapulmonary loculation".



Fig. 4: Left lateral decubitus view interpreted to show infra-pulmonary loculation of fluid.

This film (Fig. 5) of the abdomen, supine, suggests some mottled density above the gas-dilated hepatic flexure. Perhaps I should mention that in the X-ray request the clinical impression was "Subdiaphragmatic abcess versus liver metastases". This is an erect view of the abdomen (Fig. 6) showing the mottling to better advantage. It is certainly outside of the colon and seems to be associated with a mass. The X-ray impression was (1) Reflex ileus; (2) Gangrenous cholecystitis.

Dr. Zimmerman:

In considering causes of pain in the right upper quadrant of this sort, I won't bore you with excluding the possibility of unrelated gall bladder disease as I think

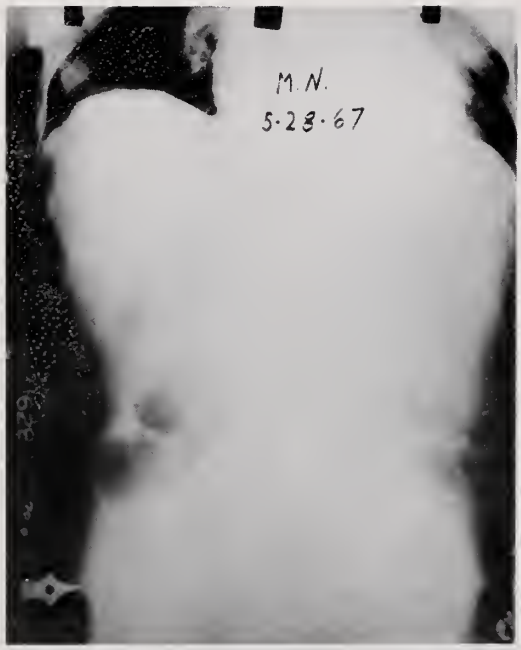


Fig. 5: X-ray of the abdomen suggesting the presence of mottled density above the hepatic flexure.

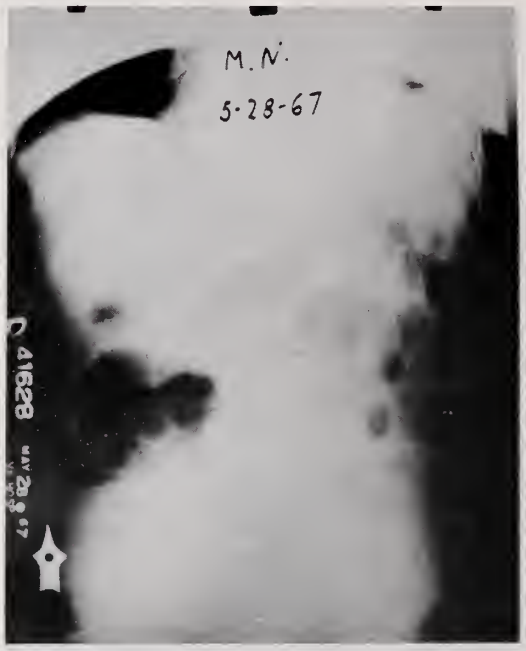


Fig. 6: Erect view of the abdomen shows localized mottling better.

that's not very relevant to the current problem. Certainly one needs to consider extensive carcinomatosis; however, it is rare for such severe pain to result from metastatic carcinoma unless growth has been extremely rapid and in this case the physical findings would have been very different. Obviously, infection was the first consideration in a patient with fever, pain and leukocytosis, all developing rapidly. An abscess either of the liver, of the subphrenic space or the subhepatic space had to be considered. Hepatic and subphrenic abscess seem less likely than subhepatic. Absence of demonstrable right hydrothorax is unusual in a patient with right subphrenic abscess. Furthermore the rarefaction and mottling that Dr. Ehrlich described for you was subhepatic and not suprahepatic. Similarly, lack of elevated alkaline phosphatase levels militated against the hepatic abscess. Nevertheless, hepatic abscess cannot be dismissed since the presence of an elevated right leaf of the diaphragm would have been more consistent with hepatic or subphrenic abscess. The subhepatic localization of the rarefaction, mottling and the lack of hydrothorax, however, seem more consistent with subhepatic abscess. Accordingly, from among the three possible sites for abscess, I selected the subhepatic.

A separate consideration is the possible cause of the left hydrothorax. Quite possibly this reflected another bout of pulmonary infarction. However, the fact that this appeared to be an infra-pulmonary effusion, as Dr. Ehrlich demonstrated for

you, led me to consider strongly the possibility of disease of the left upper quadrant of the abdomen. With an abscess on the right, an abscess on the left also warrants consideration.

From where might the abscess have come? One may speculate that this patient who had had an 85% gastrectomy might have developed with the assistance of steroids in large doses, an ulcer with rupture, which then led to abscess involvement in the right suphepatic and in the left subphrenic space.

Accordingly, we could suggest that the following sequence might have occurred (Fig. 7): Carcinomatosis accompanied by an autoimmune response and dysproteinemia somehow led to amyloidosis of the kidney and to the nephrotic syndrome. I

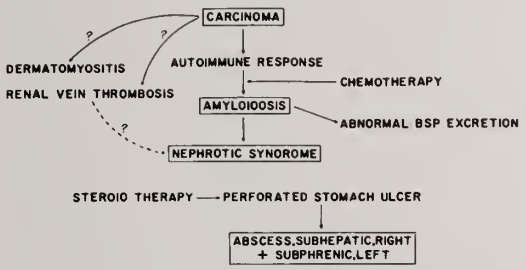


Fig. 7: Diagramatic representation of patient's illness

am sure you are familiar with the fact that nitrogen mustard therapy can accentuate the development of amyloidosis in experimental animals and apparently in patients. It is quite possible that the chemotherapy used here also might have played the same role and contributed to the rapid development of amyloidosis. I would like to propose that amyloid involvement of the liver accounted for the BSP retention. This is not to say that he could not have had renal vein thrombosis as well as amyloidosis. Whereas renal vein thrombosis occurs in less than 1% of patients with carcinomatosis, it occurs in 12% of patients who have carcinomatosis and secondary amyloidosis. If that were the case, it would explain the fact that the nephrotic syndrome developed abruptly. Amyloidosis may develop in less than a year, but the very rapid development of nephrotic syndrome here would certainly have been abetted by renal vein thrombosis. Did he have additionally another type of autoimmune response of carcinoma, namely, dermatomyositis syndrome? After raising the question I don't think I can dismiss it or support it. The terminal episode (phase 3) would be reasonably relatable to the perforated ulcer leading to the right subhepatic and left subphrenic abscess on this patient.

It is in phase 2, when he came in with the nephrotic syndrome that he had some biochemical abnormalities that don't add up into a single unit. For example, the normal BUN. In a patient who has a nephrotic syndrome due to amyloidosis, some azotemia is usual but is not mandatory. About half of the patients with renal amyloidosis come in with azotemia, and half will first present without it. I would have dismissed it, but what did bother me additionally was that he had a uric acid level of 9 mg and an inorganic phosphorus of 7 mg %. Uric acid elevation occurs with renal failure, but one would expect renal failure to have led to an abnormal BUN in order to explain hyperuricemia on that basis. So I comforted myself by assuming that the bone marrow was recovering from the inhibition by the chemotherapeutic agent and increased cell turnover had led to the hyperuricemia. But that leaves the high inorganic phosphorus level unex-

plained. A value that high means either hypoparathyroidism or renal failure. He does not have hypoparathyroidism. Accordingly, one must assume then, that he had renal failure, unfortunately, to conclude that the BUN value was either erroneous, or that this is a very unique case.

Another poorly explained feature was the hypernatremia with a serum sodium level of approximately 145 mEq/L. Dehydration due to lack of water intake could account for hypernatremia and hyperosmolality, but I would guess that he wasn't so sick or so terminal that he was no longer drinking water. One may see hypernatremia occasionally as a result of disproportionate water loss, due to intracranial disease and due to renal lesions. Its meaning in this patient is obscure.

One other aspect that bothers me is the persistent hint at eosinophilia. He had 3% of 14,000, equivalent to more than 400 eosinophiles/cubic millimeter. Subsequently, at a time that the total leukocyte count was 24,000 and one would expect eosinopenia with such a marked leukocytosis, our patient still had 2% eosinophiles. In a patient with leukocytosis, one must suspect a cause for any degree of eosinophilia. In this area one needs to consider tropical disease. We know that schistosomiasis occurs here but I see no reason other than the geographic one to consider that diagnosis in this circumstance. Now, how about other parasitic diseases? How about ascariasis, for example? I have no reason to consider that at all, other than the fact that there's a little eosinophilia, and we are here, and I am looking for things that might be troublesome. Well, if there were any such parasitic complication, it would only be an additional frill for the other diagnoses as I see them.

*Dr. Julio V. Rivera:**

I want to apologize to Dr. Zimmerman about the fact that there was an additional BUN which was elevated, which was not included in the case summary.

*Dr. Ramírez de Arellano:***

This man had a poorly differentiated carcinoma of the stomach in areas showing squamous cell metaplasia. Review of the surgical specimen showed that one of the regional lymph nodes contained metastatic cancer. However, at the time of necropsy there were no metastases,, recurrence or residual cancer. The lymph nodes were depleted of lymphocytes as compared with the lymph nodes in the surgical specimen, a change which is obviously the result of steroid therapy.

The kidneys weighed 120 grams each and were pale, yellow and somewhat granular. The gross appearance suggested either membranous glomerulonephritis, or diffuse subacute glomerulonephritis. Histologically there was lobulation of the glomerular tufts and focal thickening of the basement membrane. The glomeruli appeared ischemic and there was proliferation of the endothelial and epithelial cells. PAS and a silver stain showed focal thickening of the basement membrane and widening of the reticular material in the mesangium. An occasional epithelial crescent was found (Fig. 7). Proteinaceous

* *Assistant Chief, Medical Service and Chief, Radioisotope Service.*
** *Assistant Chief, Laboratory Service*

material was present in Bowman's spaces and convoluted tubules, together with vacuolization and hyaline granular generation of the tubular epithelium. Foamy histiocytes were frequently encountered beneath Bowman's capsule. Transition of hypercellular glomeruli to hyalinized, sclerotic glomeruli were easily demonstrated. Arterial and arteriolar sclerosis was also evident. The histologic findings in the kidneys were therefore, those of subacute and chronic membranoproliferative glomerulonephritis. The possibility that FUDR may be responsible for the glomerulonephritis was considered. However, I am not aware of any previous reports in which FUDR was to blame for renal changes of this kind.

The abdominal findings were of great interest. There was a small abscess below the left lobe of the liver in close relation to the duodenal stump and the head of the pancreas. There was no evidence of perforation of an abdominal viscus. A pure growth of *Streptococcus viridans* was obtained from the abscess. There was also an accumulation of fibrinopurulent exudate between the right diaphragm and the dome of the liver. This process obviously developed in the postoperative period following drainage of the subhepatic abscess. Examination of the thoracic cavity showed accumulation of approximately 500 to 600 ml of clear light yellow fluid in each pleural space. The lungs were severely edematous and the right upper lobe was the site of a rather extensive bronchopneumonia.

The most striking pathologic findings were in the gastrointestinal tract. Histologic sections of the remaining portion of stomach and of the proximal jejunum near the anastomosis showed a large number of rhabditiform larvae of *Strongyloides stercolaris* in the lumen, as well as embryonated eggs in the crypts of the gastric and jejunal glands, and in the lamina propria (Fig. 9). Numerous filariform larvae are seen within lymphatics in the submucosa, muscularis and serosa of the jejunum. A section of the colon also shows filariform larvae within venules and lymphatics. The mesenteric lymph nodes contain numerous larvae in the perinodal lymphatics (Fig. 10) and subcapsular sinusoid. A section of the liver shows a filariform larva (Fig. 11) within a sinusoid which has not provoked any significant inflamatory reaction. Fragments of larvae were also identified in the lungs and mediastinal lymph nodes. A significant finding was the absence of an inflamatory reaction associated with these larvae, other than the usual reaction in the intestinal mucosa.

It seems most probable that this patient had strongyloidiasis at the time of his first admission. This type of parasitosis is usually well tolerated. At any rate, none of the sections of the resected stomach and lymph nodes show evidence of strongyloidiasis. This case is similar to others (1) reported in the literature in which the host-parasite relationship was altered in favor of the parasite as a result of treatment with steroids, in which cases the autoinfection mechanism which perpetuates the cycle of this parasite was accelerated and gave rise to migration of a large number of filariform larvae through the wall of the intestine to distant sites in the body. These larvae may carry infection to the lungs and to the meninges (2). This could have been the cause of the pneu-

monia in this case; however, this cannot be proven. For one thing, we do not know what organism produced the pneumonia and it is also well-known that patients with the nephrotic syndrome are anyhow extremely susceptible to infections. The possibility of a larva migrating to the subhepatic area and producing an abscess was also entertained, but could not

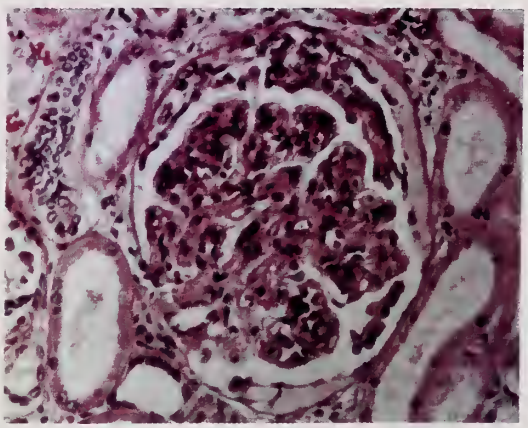


Fig. 8: Epithelial crescent in membranoproliferative glomerulonephritis.

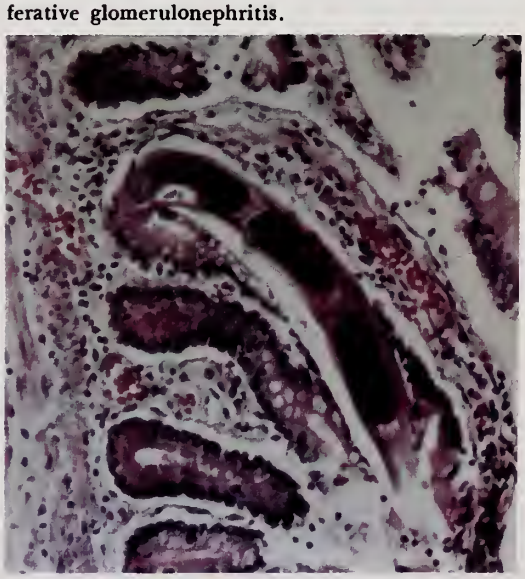


Fig. 9: Adult female *Strongyloides* worm laying eggs in jejunal mucosa.

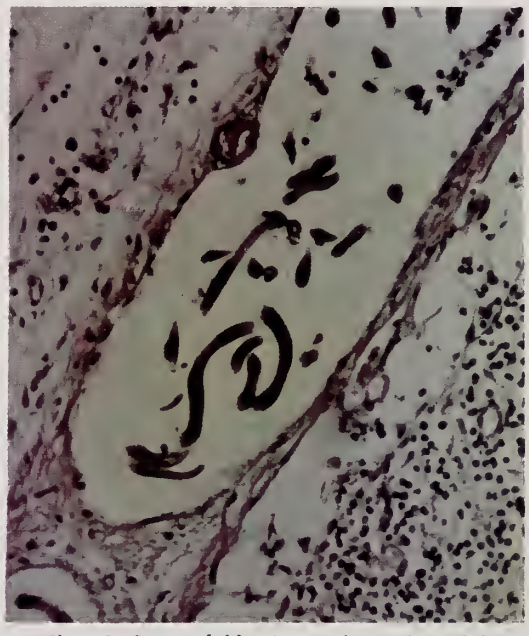


Fig. 10: *Strongyloides* larvae in perinodal lymphatic of mesenteric lymph node.

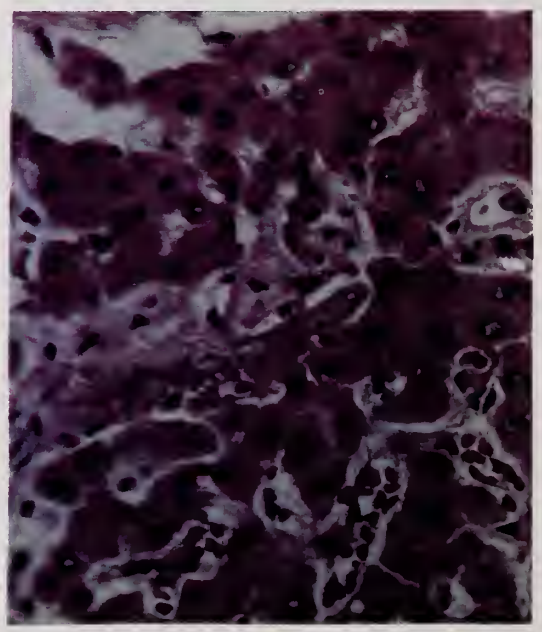


Fig. 11: Filariform larva in sinusoid of liver. Note absence of inflamatory reaction.

be proven either. The organism cultured from the abscess also makes this an unlikely possibility. The fact that *Strongyloides stercolaris* is presently known to be an opportunistic nematode following treatment of malignancy (3) with immunosuppresive drugs, indicates that in those areas where this parasitosis is endemic infestation with this parasite should be ruled out prior to undertaking prolongued treatment with steroids.

Anatomical Diagnoses

1. *Strongyloidiasis, hyperinfective phase.*
2. *Chronic membranoproliferative glomerulonephritis.*
3. *Acute peritonitis, localized, right upper quadrant.*
4. *Subhepatic abscess, small.*
5. *Bronchopneumonia, right upper lobe.*
6. *Carcinoma of the stomach, post-gastrectomy.*

Dr. Rivera:

Dr. Zimmerman was worried about the eosinophiles and I guess he was just right on that. I wonder if he would like to make a final comment.

Dr. Zimmerman:

This is a beautiful demonstration of a fantastic lesion. I have never seem anything like that before and I certainly agree with your citation literature on the effect of steroids on stronglyloidiasis as it does have on other host-parasite relationships. With regard to the renal lesion this patient should not have had membranous nephritis; he should have had amyloidosis.

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EDITORIAL

SHARING VETERANS ADMINISTRATION RESOURCES

The practice of medicine is very old, and what we are doing now has undergone a slow, individualized evolutionary development. As recently as the early years of this century, medical knowledge was so limited that an individual physician could treat most illnesses for which treatment was available, and a single practitioner frequently cared for several generations of the same family or an entire community for the span of his practice. Care was usually provided in the patient's home or doctor's office. Hospitals were reserved for mortally ill or the indigent.

Medicine has undergone many radical changes. Continuous care from a single physician is becoming increasingly rare. Almost all new practitioners are specialists and are supported by a variety of skilled personnel. Medical services are fragmented by disease categories and methods of treatment. The place of care is moving steadily from the home to the physician's office and, increasingly, to the hospital. Medicine has participated in the general explosion of science and technology, and possesses cures and preventives that could not have been predicted even a decade ago. However, the organization of health services has not kept pace with advances in medical sciences or with changes in society itself. Medical care is a complexity of many things. There is a great deal of overlapping, duplication, great gaps, high costs, and wasted effort. An integrated system in which needs and efforts are closely woven has to be worked out. Reorganization and changes are needed in the rapidly changing concept of total medical care and we must put the needs of the patients first.

A truly integrated health service system should be organized under a variety of auspices including physicians in the private practice, universities, hospitals, voluntary agencies, and government. This system should include, but not be limited to, programs which are comprehensive, serve a cross-section of socio-economic groups on a community or area-wide basis, and emphasize organized services for ambulatory patients.

Costs have risen sharply from levels that already prohibit care for some and create major financial burdens for many more. This is a situation which should not be allowed to continue.

If space, equipment, and personnel are continued to be employed in the present manner and within the present patterns and systems of care, we will not avert or even perhaps alleviate our present needs.

In putting the sharing program into effect the Veterans Administration is

seeking means of using present professional personnel and facilities more efficiently. The success of this program will mean that the availability and quality of health care for the entire community will meet the needs of all citizens and the cost of the care will be kept within reasonable bounds. Based on these principles, our plans for the fututre will have to be formulated more wisely.

We have come to realize that government alone cannot be expected to solve the problem of health care for all the people. The combined resources and experience of others outside government is also needed. This includes the professionals, voluntary agencies, religious and education institutions, all types of hospitals, organized labor, business and industry, and concerned citizens.

Towards this total effort the Veterans Administration has been authorized to join with non-federal hospitals in a cooperative effort to utilize more effectively medical resources available in the community. By especialized medical resources we mean medical resources, whether equipment, space, or personnel, which because of cost, limited availability, or unusual nature, are either unique in the medical community or are subject to maximum utilization by permitting hospitals to exchange the use of such resources. By hospital we mean a medical school, or other medical installations having hospital facilities, or Federal, State, local or other business and private hospitals.

The Veterans Administration up to now has had limited authority to use facilities of non-VA hospitals. This new legislation permits a more liberal policy on-an-exchange-of-use principle. Whenever the need exists directors of Veterans Administration hospitals are authorized to make arrangements to implement agreements between VA hospitals and other hospitals in the sharing of specialized medical resources as already described. This is done to strengthen and improve VA hospital operations through a sharing agreement.

Directors are authorized to negotiate proposed agreements with officials of medical schools, research centers, and hospitals to provide for use by-patients. of these institutions any advanced medical techniques and medical resources in the VA hospitals which are not being used for care of VA patients to maximum effective capacity.

Before the VA can utilize non-VA hospital resources under the provisions of this law, the VA must agree to provide the use of a resource to the non-VA hospital. To accomplish this, an exchange-of-use-agreement must be negotiated. This exchange-of-use-agreement is different from the mutual use principle in which the VA will agree to provide to the community hospital a resource in the VA hospital which is in excess of the needs of veterans.

In the mutual use program, primary emphasis will be directed to outpatient diagnoses and care. Inpatient care may be provided, however, usually on a short-term basis.

We in the Veterans Administration feel that this type of arrangement will

bring about the elimination of needless duplication of certain sophisticated services in the same community, which will result in benefit to all its citizens.

J. Chaves-Estrada, MD

COLORES EN EL BOLETIN

Recientes adelantos en las técnicas de litografía permiten la reproducción de ilustraciones en colores a un costo razonable. En el caso de artículos médicos la reproducción en color es de particular utilidad en la presentación de secciones histológicas y lesiones dermatológicas.

Por primera vez en este número del Boletín se presenta material fotográfico a todo color ilustrando un raro caso de infección generalizada por el usualmente inofensivo parásito Strongyloides stercolaris. Esperamos que esta innovación sea estímulo para la presentación en el Boletín de otros casos igualmente interesantes.

Julio V. Rivera, MD

ACTUALIDADES MEDICAS

New Charity to Fight Ancient Medical Mystery

Two million Americans —by conservative estimate— have epilepsy. Yet, startlingly few persons are aware of little more than the fact that the disorder exists.

For years, two respected organizations —The Epilepsy Foundation and Epilepsy Association of America— have been working vigorously to aid these two million forgotten Americans. Individually, they have done much to shed lights on this greatly misunderstood disorder. But a wide gap remained between what they could acomplish separately and what could be achieved by joining forces.

Now, with the merger of the two groups into the single framework of Epilepsy Foundation of America, the dream of a strong, national voice that will speak out in behalf of these two million Americans has become a reality.

For the first time, there is an agency with sufficient resources for a concentrated assault on the immense problems confronting those with epilepsy in every community. Medically, these problems take various forms.

To begin with, while it is now possible for 80 percent of those with epilepsy to achieve seizure control, the disorder largely remains a mystery to the medical profession. Major research questions are yet unresolved:

—What starts a seizure?

What happens, chemically, in the brain cells during a seizure?

What enables a seizure to spread, as it sometimes does, until it involves the entire brain?

—How do anti-convulsant drugs work, and what effect do they have on the brain?

—Is there a cure, or a drug that will prevent the possibility of seizures in all patients?

In addition, there is a need to develop new and better drugs, and a necessity for further study into the psychological and environmental aspects of seizure control.

With the formation of Epilepsy Foundation of America comes the expanded opportunity to provide "seed" grant support with an aim toward stimulating fresh thinking among research organizations and individual scientists.

Too often, the young or relatively unknown investigator who has an interesting hypothesis stands a poor chance of winning the support of large grantors of research monies. Here, Epilepsy Foundation of America has an opportunity to be the nimble catalyst, ready to take a chance on an unproved but interesting theory or an untried investigator. It was in just such manner that the research leading to the life-saving cancer diagnostic tool, the Pap smear test, began.

In addition, Epilepsy Foundation of America is now in a position to enlist the support and cooperation of the pharmaceutical industry in an effort to develop

fresh approaches leading not only to better seizure control techniques, but hopefully, to the eventual prevention and cure of epilepsy and related brain disorders.

Improved diagnostic and treatment facilities are also needed in most parts of the country—a goal that the new agency will be able to work toward with previously impossible force and energy.

The early detection of epilepsy is essential to its proper treatment. Yet, the World Health Organization has estimated that only one in five Americans with epilepsy is receiving the necessary medical care. The villain in this particular tragedy is the social stigma associated with epilepsy which leads many persons to conceal their disorder.

But there are other important roadblocks to adequate diagnosis and treatment. One is that those in the best position to detect epilepsy in its earliest stages—parents and teachers—generally have neither the experience nor the basic knowledge to do this.

Certainly, early detection and treatment are necessary to prevent many of the psychological burdens that so often accompany the disorder and keep epilepsy patients from playing a productive role in the community.

The Epilepsy Foundation's "School Alert" program, aimed at increased teacher, parent, and student awareness of all aspects of epilepsy, was a giant step toward early detection. But it is estimated that one in every 50 children has epilepsy. That means that there are many, many more parents and teachers who must be reached, and reached effectively.

Through the chapters of Epilepsy Foundation of America, the "School Alert" program will be expanded and additional public information campaigns will be launched as part of an aggressive, year-round program designed to reach the American people with epilepsy information on a scale never before possible.

The treatment of epilepsy too often consists almost solely of an effort to arrest or control seizures. Most patients with epilepsy really require a whole range of interrelated services—from psychotherapy to vocational rehabilitation. These must be a part of the patient's treatment if he is to make satisfactory progress.

Right now, however, there are too few qualified "paramedical" personnel available—trained EEG technicians, clinically-oriented psychologists, social workers and others.

The voluntary movement against epilepsy, through Epilepsy Foundation of America, is now in a position to foster and support greatly improved training standards for paramedical personnel, and to encourage more people to enter into these medically-related specialties.

Equally important, Epilepsy Foundation of America will now have the resources to assume a prominent role in providing for the day-to-day informational needs of the nation's physicians—particularly those not trained in neurology or other disciplines related to epilepsy. Epilepsy Foundation of America will also assist doctors in obtaining up-to-date information on every aspect of diagnosis and therapy.

Finally, more — and more adequate treatments centers are needed, both in-patient and out-patient. Here the role of Epilepsy Foundation of America is clear. Working through its extensive network of

chapters across the country, it can now help to develop facilities for total care and treatment, not only for those requiring constant custodial care, but also for the vast majority who can be rehabilitated.

Who will benefit? The two million Americans who have epilepsy will, of course. But so will every citizen of every community in the nation.

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NOTICIAS

Locales

Abril 16 — Asamblea General AMPR.
Abril 20 — Primera sesión ordinaria — Cámara de Delegados AMPR.
Julio 4-7 — Convención Semi-Anual AMPR.

VACANCY ANNOUNCEMENT

MEDICAL OFFICER (GENERAL PRACTICE) GS-602-12, $13,753 to $17,191 per annum plus 5% COLA — Code No. Allen-261, needed at US NAVAL RADIO STATION, Fort Allen, P. R.

DUTIES: Serves in the capacity of a general practitioner of medicine and surgery in a Naval Radio Station Dispensary which receives military personnel, military dependents, Civil Service employees, certain government employee dependents who reside on board the station, station employees, and other persons who visit the station as authorized guests or for other reasons.

Submit a completed Standard Form 57, "Application for Federal Employment", directly to the Industrial Relations Officer, US NAVAL STATION, BOX 8, SAN JUAN, P. R. 00932 indicating CODE NO. and TITLE of this position.

PREMIO
DR. RAMON RUIZ ARNAU

La Asociación Médica de Puerto Rico presenta el premio "Dr. Ramón Ruiz Arnau", para reconocer el periodismo que contribuye a un mejor entendimiento público de la medicina y la salud en Puerto Rico. El premio es dado en memoria del fallecido Dr. Ramón Ruiz Arnau quien fuera primer Director del Boletín Médico de la Asociación Médica de Puerto Rico.

El propósito de este Premio ese alentar a todos los periodistas a instruirse en el arte de reportar noticias médicas de manera que el pueblo pueda ser educado mejor y estar al tanto de los adelantos de la ciencia médica y de las necesidades de salud pública.

Cualificaciones

1. Los interesados deben llenar la forma de aplicación oficial.

2. El récord del aspirante debe reflejar un reportaje sobresaliente en el campo de las ciencias y la salud.

3. Este reportaje debe haber aparecido en uno de los medios de comunicación de Puerto Rico durante los 6 primeros meses del año 1968. La fecha límite para presentarlos será el 30 de agosto de 1968.

4. La persona nominada debe ser empleado de uno de los medios de comunicación de Puerto Rico.

5. La solicitud puede ser hecha por un artículo o programa o por una serie de artículos o programas.

6. Todas las solicitudes deben venir acompañadas de un recorte, cinta magnetofónica o película. Las cintas y películas serán devueltas si así se requieren.

7. Todas las solicitudes deben venir acompañadas de la siguiente información: Título de entrada, escritor o productor, publicación en la cual el artículo o programa apareció o estación o cadena por la cual el programa fue transmitido, fecha en que fue publicado, radiodifundido o televisado, nombre, dirección y título de la persona que lo somete.

La evidencia tangible de este Premio serán $100.00, una placa inscrita apropiadamente la cual será entregada en el lugar y fecha que señale el Comité Adjudicador, y un viaje a la Convención Clínica de la Asociación Médica Americana.

Fallo

Los trabajos serán juzgados a base de: 1) exactitud; 2) calidad; 3) estilo; 4) materia seleccionada y 5) interés público e impacto. El Comité Adjudicador estará compuesto de: un representante por cada uno de los medios de comunica-

ción; el Presidente, o su representante, de la Sociedad de Relaciones Públicas de Puerto Rico, el Presidente del Consejo de Relaciones Públicas de la AMPR, el Presidente de la Junta Editora del Boletín Médico de la AMPR y el Presidente de la AMPR.

NEW BOOKS

Other books received by the University of Puerto Rico School of Medicine and School of Dentistry.

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1. Harkavy, Joseph. Vascular allergy and its systemic manifestations. Washington, Butterworths, 1963.
2. Masturzo, Aldo. Cybernetic medicine. Springfield, Ill., C. C. Thomas, 1965.
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Public Health

1. Gómez, Escamilla. Principios fundamentales de educación sanitaria. México, D.F., Editorial F. Trillas, S.A., 1967.
2. Hinman, E. H. World eradication of infectious diseases. Springfield, Ill., C. C. Thomas, 1966.
3. Kiser, Clyde V. Estudios de demografía. New York, La Fundación Milbank Memorial con la colaboración de Fundación Interamericana de Bibliotecología Franklin, Buenos Aires, 1967.
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1. Adams A.R.D. Clinical tropical diseases. 4th ed. Phila., F. A. Davis Co., 1966.
2. Manson-Bahr, Sir Philip Henry. Manson's tropical diseases. 16th ed. Baltimore, William & Wilkins Co., 1966.
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Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

June 19-21 — Infectious Disease: Mechanism and Manifestations, University of Maryland School of Medicine, Baltimore, MD.

Sep. 26-29 — The Metabolic Basis of Heart Disease, Wayne State University School of Medicine, Detroit, Mich.

Oct. 7-11 — Basic Mechanism in Internal Medicine, Medical College of Virginia, Richmond, Va.

Oct. 7-11 — Computers in Medicine, University of Wisconsin Medical Center, Madison, Wis.

Oct. 21-25 — Current Concepts of Neurology — Diagnosis and Treatment, University of Maryland School of Medicine, Baltimore, Md.

Oct. 28 - Nov. 1 — Rheumatic Diseases: Pathology, Diagnosis and Treatment, Robert B. Brigham Hospital, Boston, Mass.

OTHER MEETINGS

May 19-20 — First International Symposium on Dextrans, to be held at Galveston Island, Texas, entitled CURRENT CONCEPTS OF THE BASIC ACTIONS OF DEXTRANS AND THEIR CLINICAL APPLICATION IN THE CARDIOVASCULAR AND RELATED FIELDS.

July 22-23 — Air Pollution Medical Research Conference, Denver, Colo., Denver-Hilton Hotel, all day.

Aug. 26-29 — Council on Foods and Nutrition, Western Hemisphere Nutrition Congress II. Cosponsors: American Institute of Nutrition; Latin American Nutrition Society; Nutrition Society of Canada, San Juan, Puerto Rico, Americana Hotel.

Sept. 5-7 — Board of Trustees, Chicago, Ill., AMA Headquarters.

Sept. 7-8 — Residency Review Committee for Obstetrics-Gynecology, Hot Springs, Va., Homestead Hotel, 2:30 p.m.

Sept. 27-28 — Council on Occupational Health, New York, N.Y., Waldorf-Astoria Hotel, 9:00 a.m.—5:00 p.m.

Sept. 29 — Council on Occupational Health with representatives of State Medical Association Committees on Occupational Health, New York, N.Y., Waldorf-Astoria Hotel, 9:00 a.m. — 5:00 p. m.

Sept. 30 - Oct. 1 — 28th Annual AMA Congress on Occupational Health, New York, N. Y., Waldorf-Astoria Hotel.

Oct. 2-3 — Fourth National Congress on Health Quackery, Chicago, Ill., Drake Hotel.

Oct. 4 — Legal Conference for Medical Society Representatives, Chicago, Ill., Drake Hotel.

Oct. 5-6 — Second National Congress on Medical Ethics, Chicago, Ill., Drake Hotel.

Oct. 11-12 — Council on Mental Health, Chicago, Ill., Drake Hotel.

Oct. 24-27 — Board of Trustees, Chicago, Ill., AMA Headquarters.

Oct. 25-26 — Residency Review Committee for Anesthesiology, DGME, Atlanta, Ga., Regency-Hyatt House, 9:00 a.m.

Internacionales

• *VI Congreso del Colegio Internacional Neuro-Psico-Farmacológico.* — Costa del Sol, España; abril 1968; (Prof. Francisco Valdecasas, Calle Casanova 143, Barcelona 11, España).

• *Simposium Oseo de la Asociación Europea de Radiología.* — Londres, Inglaterra; 4-6 abril 1968; (Dr. J. S. MacDonald, c|o Conference Office, 156 Lamberth Road, London S. E. 1, Inglaterra).

• *VIII Congreso Interamericano de Cardiología* — Lima, Perú; 21-27 abril 1968; (Dr. Dante Peñaloza, Pablo Bermúdez 274 - Of. 705-706; Lima, Perú).

• *VI Congreso Mundial de Fertilidad y Esterilidad.* — Tel Aviv, Israel; 20-27 mayo 1968; (Dr. N. Soferman, P.O.B. 26102, Tel Aviv, Israel).

• *VII Congreso Internacional de la Academia Internacional de Patología.* — Milán, Italia; junio 1968; (Prof. Alfonso Giordano, Instituto D'Anatomie Patologique, Universitá di Milán, Via Francisco Sforza 38, Milán, Italia).

• *X Reunión Anual del Colegio Internacional de Angiología.* — Ginebra, Suiza; 23-28 julio 1968; (International College of Angiology, 381 Park Avenue South, New York, N.Y. 10016, EE.UU.).

• *XII Congreso Internacional de Biología Celular.* — Bruselas, Bélgica; agosto 1968; (Prof. P. Dustin, Institut D'Anatomie, 97 Rue aux Laines, Bruselas, Bélgica).

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g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

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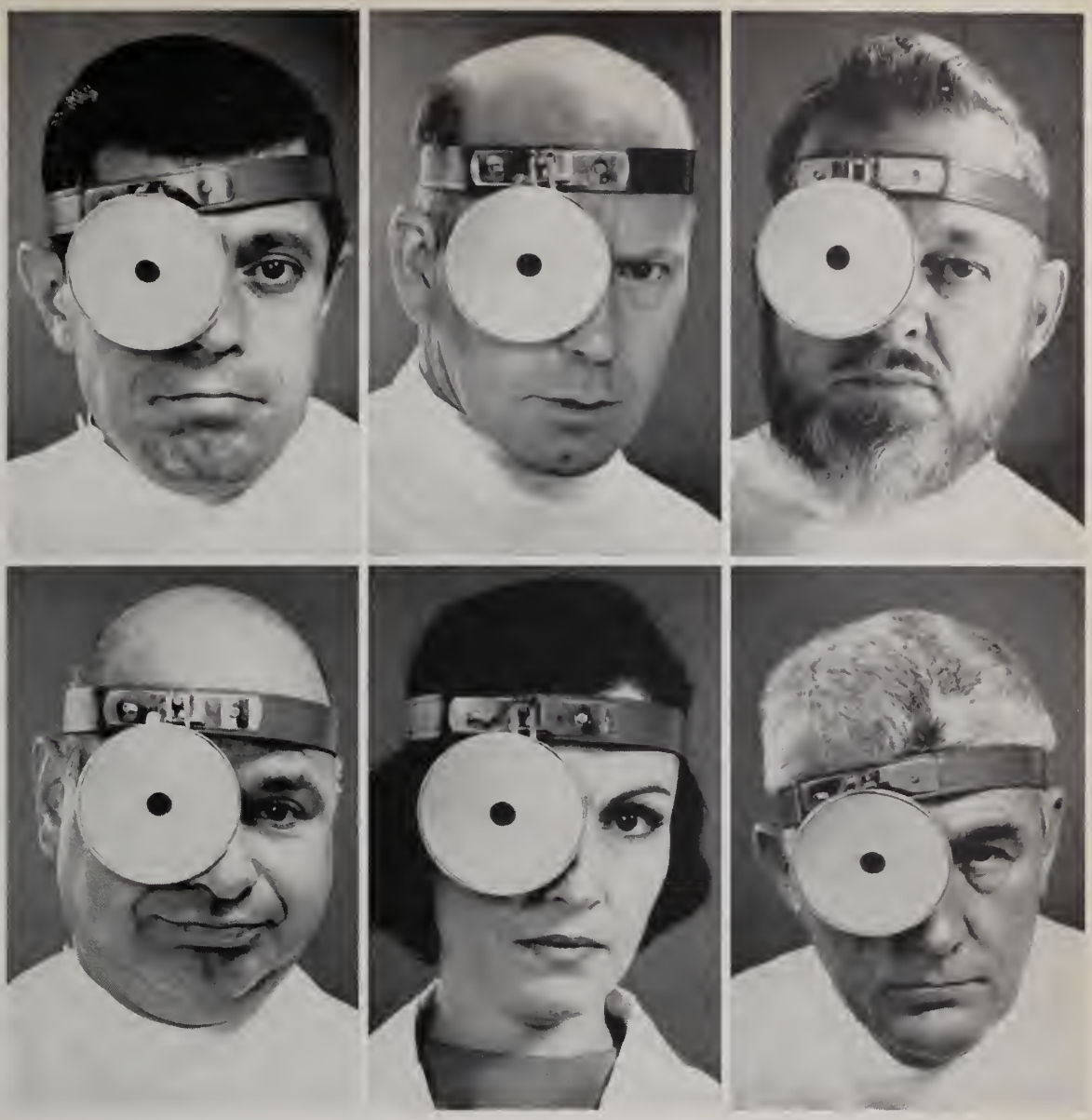
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Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.,* operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

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Histaspan keeps protecting against pollinosis...

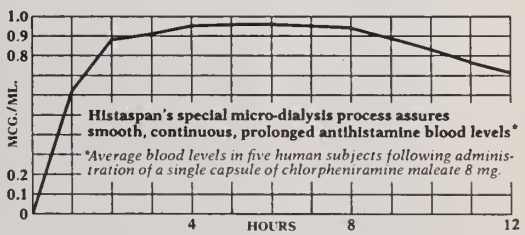
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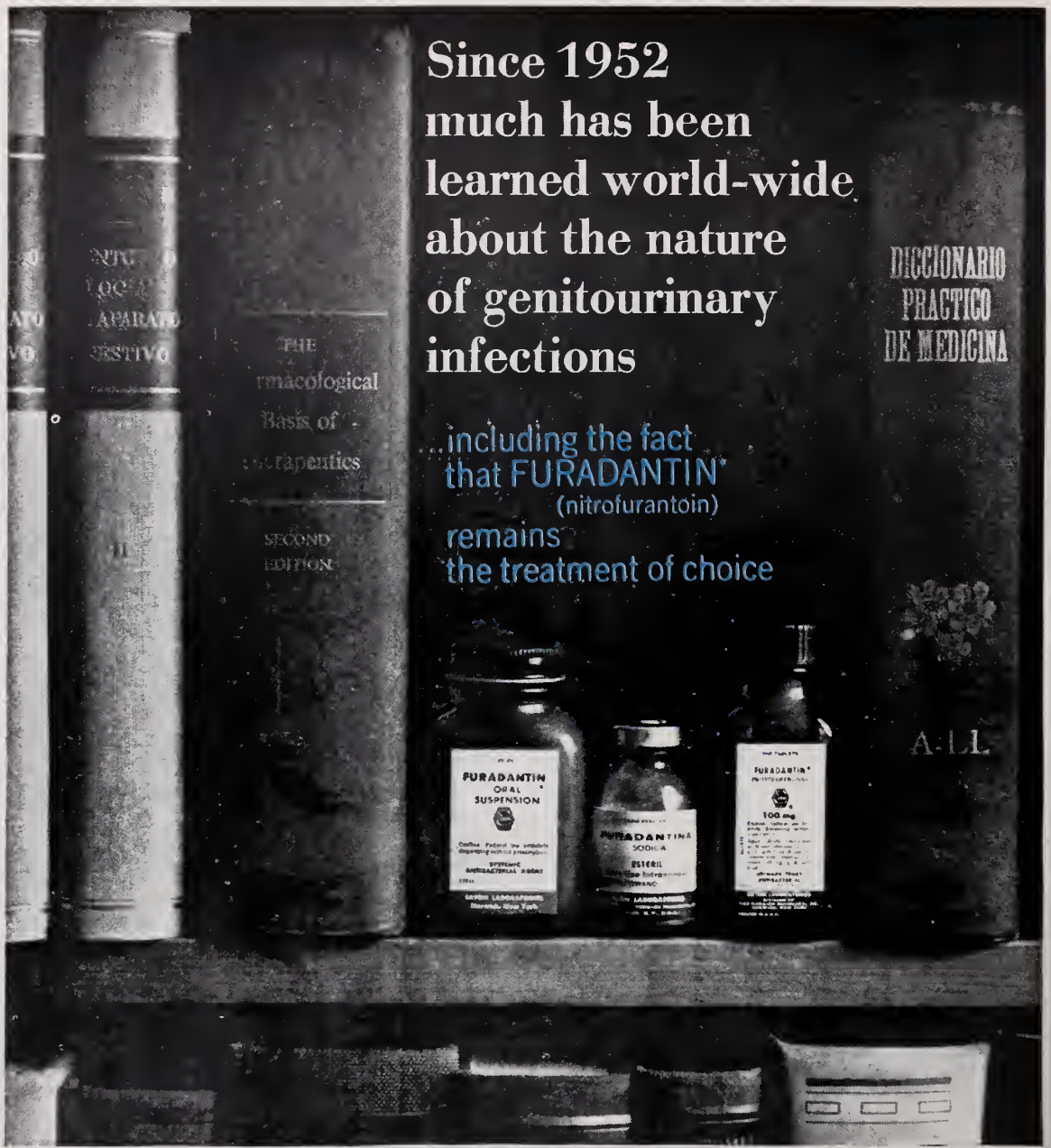
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Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of Tofrānil and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before Tofrānil may be substituted. Initial Tofrānil dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, Tofrānil should not be used during the first trimester of pregnancy.
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Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment with Tofrānil. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing Tofrānil for patients with increased intraocular pressure.
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The drug is not recommended at present time in patients under 12 ar of age.
Adverse Reactions: Dryness of th mouth, tachycardia, constipation, s- turbances of accommodation, sw- ing, dizziness, weight gain, urinar frequency or retention, nausea ar vomiting, peripheral neuritis, milc parkinson-like syndrome, tremors rare cases of falling in elderly pa- tients, confusional states (with su symptoms as hallucinations and c- orientation), activation of psycho in schizophrenics and agitation (inc l-

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Weariness "without cause"



Psychic tension with depressive symptomatology?

"For weeks I've done practically nothing and I'm always tired. I wake up tired and I go to bed tired. It's really absurd."

When the patient complains of fatigue, and you can find no organic cause, you recognize that it may serve her as a means of avoiding responsibilities or facing an emotional problem. It is, in effect, a psychological retreat behind a somatic cover of continuous fatigue —one of the many depressive symptoms often associated with psychic tension.

She needs counsel and reassurance, and perhaps a tranquilizer to attenuate excessive tension and help restore the capacity to cope. As an aid to successful management, consider the value of Valium® (diazepam). As psychic tension is eased by Valium therapy, secondary depressive symptoms too may subside. The patient feels more capable, therefore more hopeful better able to handle situations of intense stress.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects —particularly with known compounds which may potentiate action of Valium, such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Employ usual precautions in the severely depressed or in those with latent depression; suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal o hepatic function. Limit dosage to smallest effective amount ir elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually a needed or tolerated).

Adverse Reactions: Side effects most commonly reported drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache hypotension, incontinence, jaundice, changes in libido, nausea changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See **Precautions.**) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg, and 10 mg; bottles of 50, 100 and 500.

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Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardíacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extrapiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

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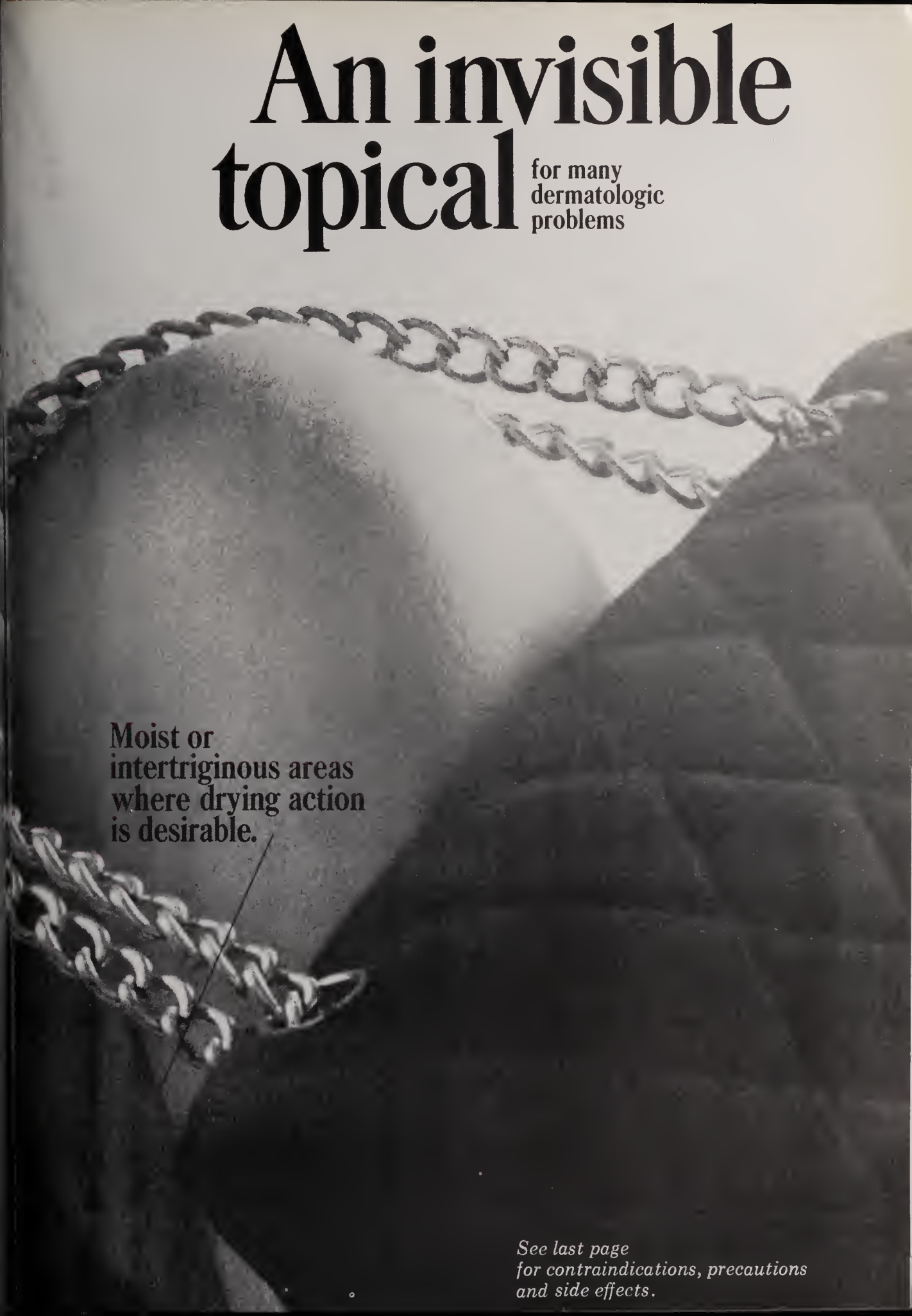
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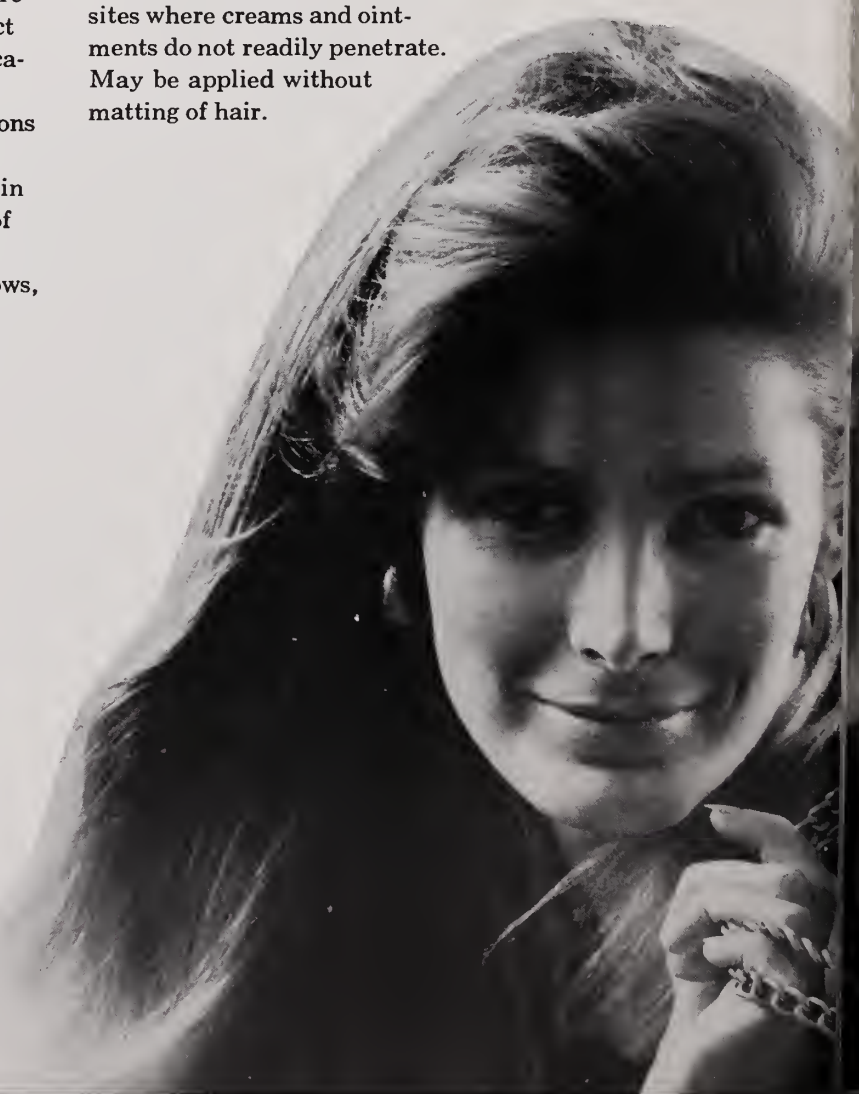
Synalar Solution produces rapid antiinflammatory, antipruritic action through its unique topical corticosteroid, fluocinolone acetonide. The propylene glycol vehicle provides additional benefits for therapy at problem sites where it is difficult to achieve contact between the lesion and medication—or where creams or ointments may make the lesions worse. Synalar Solution has proved particularly valuable in the symptomatic treatment of seborrheic dermatitis of the scalp, nasolabial folds, eyebrows, ears, and in flexural folds such as the axillae, inframammary, umbilical and anocrural areas. It has also been reported to achieve excellent results in the adjunctive management of atopic dermatitis, contact dermatitis, neurodermatitis, nummular eczema, psoriasis, and sweat retention syndromes in these problem sites.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE:
Considerations in Treatment, From Acute Respiratory Failure to Long-Term Outpatient Care

David E. Dines, MD

I like to begin the discussion of management of respiratory failure in the patient with chronic obstructive pulmonary disease with a description of the steps taken when he first comes to the respiratory care unit of the medical chest service. It seems fitting to start at the beginning, the acute respiratory failure phase, and progress to the long-term treatment program which is on an outpatient basis.

Treating Acute Respiratory Failure

In combating the physiologic abnormalities of acute respiratory failure, speed in initiating the therapeutic measures is of utmost importance. These measures include securing a patent airway, removing secretions, oxygenating the patient, and ventilating the lungs.

The most important factor in precipitating acute respiratory failure is bronchopulmonary infection (1, 2). Drugs have been found to be a major iatrogenic contribution to respiratory failure (3). Neder and associates (4) confirmed the observation that mucous plugging was a consistent finding among patients who died in status asthmaticus; they found a high degree of correlation between death and the amount of sedation received.

From the Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Read at the meeting of the Puerto Rico Medical Association, San Juan, November 14 to 18, 1967.

Treatment of acute respiratory failure must be of an emergency nature. Once a patient becomes unconscious or drowsy, cough becomes inadequate, secretions puddle, and ventilation is further embarrassed. The physiologic problems consist of maintenance of adequate breathing and expectoration and avoidance of hypoxemic hypoxia (5). Many patients are severely hypoxemic on arrival in the respiratory care unit (oxygen tension, Po_2, below 30 mm Hg and oxygen saturation below 50%); there is moderate hypercapnia (Pco_2, 76 mm Hg) and profound acidemia (pH, 7.22). *Cyanosis is an unreliable index of the state of arterial anoxemia* (6, 7). Oxygen saturation must decrease to about 74% for cyanosis to be grossly and reliably evident. Monitoring respiratory failure requires frequent measurement of arterial blood gas tensions and pH (8, 9). We are becoming increasingly aware that monitoring by the Astrup technique does not provide enough information in patients with respiratory failure (10). Repeated arterial punctures are necessary to indicate whether or not carbon dioxide is being eliminated and adequate oxygenation is being obtained. Arterial puncture is a safe and simple procedure requiring no special equipment (11).

Blood is drawn for arterial blood gas studies and chemical analyses immediately

on admission of the patient to the unit. An attempt is made to clear bronchopulmonary secretions with suction. Humidification with a heated nebulizer prevents drying out of the respiratory mucosa and adds moisture to secretions within the air passages (12). *High fluid intake is imperative* for liquefaction of secretions, and sodium iodide in a dose of 1.0 gm/liter can be administered intravenously when the patient is too ill to take fluids orally.

Since infection often precipitates an acute attack (13), a roentgenogram of the thorax is made by portable x-ray machine, and a smear and a culture are made on the sputum at the time of admission. Depending on the patient's drug allergy history, either ampicillin (500 mg every 6 hours) or tetracycline (500 mg every 6 hours) is given until the sputum culture has been reported. Frequent cultures are indicated to direct a change in antibiotic treatment.

Respiration: Oxygen therapy is an essential part of the treatment at this phase. Intermittent positive-pressure breathing for 15 minutes of every hour can often maintain stable levels of Pco_2 even when oxygen is being administered continuously. Oxygen is given by nasal cannula at 2 liters/min. (14). Adjustment of inspired oxygen concentration to provide an arterial Po_2 of approximately 50 mm Hg can prevent the lethal consequences of hypoxia and, in most cases, prevents significant hypercapnia. The respiratory depressant action of oxygen may aggravate hypercapnia in a few patients (15), and Pco_2 can increase 50 mm Hg in an hour. Because the depressant action persists after the gas is withdrawn, intermittent administration of oxygen causes more severe hypoxia than existed before the oxygen was administered (16) Campbell and Gebbie (17) have devised an oxygen mask which uses the Venturi principle to produce a constant inspired oxygen concentration. We have used the Venturi mask to provide 28% oxygen, but we more often use a nasal cannula to give 2 to 3 liters/min (18) which is adequate to increase Pao_2 levels to normal in the majority of cases. For successful oxygen therapy, it is essential that frequent measurements of arterial Po_2 and Pco_2 be made. Campbell (19) has shown that the arterial Pco_2 reveals the adequacy of alveolar ventilation:

$$\text{arterial } Pco_2 = \frac{CO_2 \text{ production}}{\text{alveolar ventilation}} \times 0.86.$$

The Pco_2 is the criterion of the adequacy of alveolar ventilation and is the best index of progress in a patient with inadequate ventilation.

There are varying degrees of severity of respiratory failure. If the patient has an increased Pco_2 but is conscious and expectorating, he is treated with intermittent positive-pressure breathing, with heated nebulization, for 15 minutes of every hour and with isoproterenol (Isuprel®) 1:200, 10 drops plus 10 drops of distilled water every 4 hours. Aminophylline, 250 mg in 500 ml of 5% dextrose in water, is administered intravenously every 8 hours as a bronchodilator and respiratory stimulant.

It is abundantly clear that intermittent positive-pressure breathing administered a few times daily is of little benefit (20). With the low-flow oxygen therapy (2 to 3 liters/min), it is our practice to administer *intermittent positive-pressure breathing for 15 minutes of each hour.*

If increasing drowsiness and an increasing Pco_2 are encountered with general worsening of the patient's condition, estab-

lishment of an artificial airway and mechanical ventilation becomes mandatory. Intubation is performed by an anesthetist (one is on emergency call at all times). Oral intubation is always used as a preliminary to tracheostomy; and, whenever a tracheostomy has to be done, it is done in the operating room, over a cuffed endotracheal tube, with absolutely sterile conditions, never at the bedside. Insertion of a tube in the tracheal stoma is reserved for those patients requiring control of ventilation for longer than 72 hours or for patients in whom the secretion problem makes it mandatory to evacuate secretions, decrease the dead space, and establish continuous artificial ventilation.

When artificial ventilation becomes necessary, intermittent positive-pressure breathing with 40% oxygen should maintain the arterial blood oxygen tension at about 100 mm Hg. Patients with arteriovenous shunting, pneumonia, or severe interstitial fibrosis need an oxygen level of 50% or more for arterial blood oxygen tensions to be 70 to 90 mm Hg. However, patients with emphysema and bronchitis will usually reach these tensions breathing 30 to 40% oxygen. Tidal volume and minute volume must be monitored to appraise the effect of the respirator. In patients on ventilators, it is important to provide 5 to 10 maximal inflations of the lungs every hour to counter the tendency of respiratory units to close (microatelectasis). Having established an acceptable level of ventilation, one must measure its efficacy by determining arterial blood gas tensions. The flow rate of the machine must be regulated to satisfy the patient's sensation of need or he will struggle against the respirator and perform more respiratory work than without it.

The entry and exit of air in all lung segments should be listened to frequently with a stethoscope. A lobe excluded from ventilation and gas exchange by plugged bronchi acts as an arteriovenous shunt. In a circumstance such as this, gas exchange is inadequate despite normal or increased minute ventilation. To improve alveolar ventilation, the rate must be slowed and tidal volume increased. Hourly blood gas analysis may be necessary to allow adjustment of ventilation to reduce the arterial hydrogen ion concentration to normal.

Respiratory Equipment: We use the Bird Mark X respirator, but there are many other makes of positive-pressure respirators which have their enthusiastic supporters (21-24).

The objective of respiratory treatment is to improve alveolar ventilation by assisted (patient-cycled) or controlled (machine-cycled) ventilation (25). There are three types of respirators: (1) pressure-cycled (intermittent positive-pressure) which can be patient-controlled or machine-controlled, (2) volume-cycled, and (3) time-cycled. Pressure cycled respirators include the Bird, Bennett, and Mine Safety machines. A valve near the mouthpiece is opened by the subject's inspiratory suction to initiate flow. Inspiratory gas flow continues until a preset release (expiratory) pressure is exceeded in the lung valve system. The flow valve closes and flow ceases; another mouthpiece valve opens, and expiration occurs to the atmosphere. The maximal pressure of 45 cm of H_2O will inflate all lungs except those that are very stiff and have extreme airway resistance. Such a respirator can be converted to controlled ventilation when the inspiratory sensitivity

is overridden by a variable air-leak timer (apnea control) so that inspiratory flow is automatically cycled.

Volume-cycled respirators use a motor-driven piston to pump air (Moerch, Emerson), and they override spontaneous breathing to provide controlled ventilation only. They cannot be used to assist ventilation.

Time-cycled machines (Engstrom Universal) use electrical pneumatic timing mechanisims. The pressure-cycled respirators (Bird Mark VII and Bennett PR-2) can be converted to time cycling.

Acid-Base Balance: In patients with severe respiratory acidosis, the reduction of Pco_2 from 100 to 60 mm Hg should be prolonged over 6 to 8 hours to prevent seizures, hypotension, and shock (26, 27). In these patients, an attempt should be made to increase the blood pH by buffering with sodium bicarbonate if the pH is 7.2 or below. We use 90 mEq (100 ml of 0.3M solution) of sodium bicarbonate given intravenously, monitoring the administration with frequent Astrup determinations. The lactic acidosis from hypoxemia or depression of renal hydrogen ion secretion and bicarbonate formation seems to be the fundamental difficulty in the failure of the buffering system to compensate for the increasing Pco_2 (28). If plasma chloride level is low, chloride should be administered to correct the chloride stores so that bicarbonate can be excreted selectively by the kidney.

Patients with chronic obstructive pulmonary disease often present with metabolic alkalosis superimposed on a chronic respiratory acidosis (29). Reduction of Pco_2 with the mechanical respirator may occur more rapidly than the body can eliminate retained bicarbonate, resulting in alkalosis even when Pco_2 values are increased (30). Shifts in potassium ion accompany the pH change and also must be dealt with (31). Blood electrolytes must be checked at frequent intervals. Alkalosis can be treated by decreasing the tidal volume, by reducing the expiratory pressure, or by adding dead space (extra tubing between the respirator valve and the patient's airway).

Possible Complications: Recent reports (32-34) of pathologic changes resembling hyaline membrane in the lungs of patients treated with mechanical ventilators and high inspired oxygen concentrations for prolonged periods point out the necessity of using the lowest inspired oxygen concentration compatible with adequate oxygenation of the patient (limit of 100 mm Hg in arterial Po_2).

It is also important to keep in mind the possibility of interfering seriously with venous return, and hence cardiac filling, by positive-pressure breathing (35). Cuffed tubes must be deflated at frequent intervals to avoid pressure damage to the trachea.

Gross contamination of aerosol equipment (36, 37) — including nebulizers and all tubing, connections, and masks — must be prevented by proper washing and sterilization to prevent bacterial colonization.

Respiratory Stimulants: Canter and Luchsinger (38) described successful treatment of respiratory failure without mechanical assistance in 18 of 22 patients using doxapram hydrochloride as a respiratory stimulant combined with oxygen therapy. They reported a decrease in Pco_2 and correction of acidosis as a result of the improved ventilation and decreased work of breathing. *Respiratory stimulants increase*

metabolism and work of breathing as evidenced by an increase in oxygen consumption (39). When the system is incapable of handling such an increase in metabolic rate, then the Pco_2 can increase even higher. It is for this reason that we *do not use analeptics in the treatment of acute respiratory failure.* Rodman and associates (40) compared aminophylline (250 mg intravenously) with ethamivan (Emivan) (50 mg intravenously) and found that aminophylline produced a greater, more uniform, and more lasting response.

Treatment After Acute Phase

The tapering off of artificial support of ventilation must be done gradually; even when withdrawal of support is completed, these patients should remain under close supervision for several days. As ambulation begins, oxygen-supported exercise (41) is of value to promote a sense of well-being and make possible greater physical independence. We begin these patients on an oxygen-supplied walker (Fig. 1) with a nasal cannula and a flow rate of oxygen of 5 liters/min for 15 minutes twice a day. We increase this each day until the patient is walking in the hospital corridor for 30 minutes four times a day. The same exercise training can be achieved with a nasal cannula and 30 feet of tubing (Fig. 2). Oxygen-supported exercise is well tolerated and can be continued by the hypoxemic patient at home (42). Long-term continuous oxygen therapy produces clinical improvement without changing mechanical lung function (43), there is decreased pulmonary arteriolar resistence after 1 month of constant exygen therapy, as well as diminished erythrocyte production.

Long Term Care

The intensive medical regimen is continued from the time the patient is admitted to the respiratory care unit. No treatment of chronic obstructive pulmonary disease can be successful without the complete cooperation of the patient. Once he has been brought out of respiratory acido-



Fig. 1. Oxygen-supplied walker used in the hospital to begin ambulation. We use a flow rate of 5 liters/min, either with a mask or nasal cannula.



Fig. 2. Exercise training utilizing 30 feet of tubing with nasal cannula (flow rate, 5 liters/min).

sis, he must be well indoctrinated in the long-term program of treatment. Smoking in any form must be discouraged.

Bronchodilators relax and dilate constricted or collapsed airways. Ventilation is improved as all parts of the lung become available for gaseous exchange. Isuprel in a 1:200 dilution and racemic epinephrine (Vaponefrin) are administered either in a DeVilbiss No. 40 nebulizer with a 501 air compressor (Fig. 3) or with a Liston-Fletcher Hand-E-Vent and air compressor (Fig. 4), using 10 drops of the bronchodilator plus 10 drops of distilled water four times a day (before meals and at bedtime). The administration of a bronchodilator by nebulizer is followed 1 hour later (after the meal) with an oral bronchodilator, such as theophylline choline salt (Choledyl), aminophylline with methoxyphenamine (Orthoxine®), theophylline-ephedrine-phenobarbital (Tedral®), theophylline-glyceryl gualacolate (Quibron®), oxtriphylline-glyceryl guaiacolate (Brondecon®), aminophylline - ephedrine - amobarbital (Amesec®), or aminophylline-ephedrine-phenobarbital (Amodrine®). An expectorant is given to liquefy secretions — either saturated solution of potassium iodide (15 drops twice a day) or glyceryl guaiacolate (Glycotuss ® or Robitussin®) (2 teaspoons three times a day). A broad-spectrum antibiotic, either tetracycline (500 mg four times a day for 5 days) or ampicillin (500 mg four times a day for 5 days) de-



Fig. 3. DeVilbiss No. 40 nebulizer with a DeVilbiss 501 air compressor through which the bronchodilator is administered.



Fig. 4. Liston-Fletcher Hand-E-Vent with air compressor, which works on the Venturi principle.

pending on penicillin sensitivity, is given when there is upper respiratory tract infection or discolored sputum. Control of infection prevents progression of the disease. It has been postulated that repeated low-grade infection of the small airways produces centrilobular emphysema (44). Patients are asked to maintain a high fluid intake, use precautions against dust, and avoid respiratory irritants. They are instructed in breathing exercises to use at home three times a day (Fig. 5). It is important to break the ineffective pattern of rapid, deep inspirations by substituting a pattern allowing sufficient time for expiration to permit adequate emptying of the lungs through their narrowed airways (45).



Fig. 5. Technician in emphysema clinic teaching a patient breathing exercises.

In patients with chronic obstructive pulmonary disease, pulmonary hypertension develops from the reduction in the pulmonary capillary bed brought about by hypoxemia and destructive alveolar changes (46). Hypoxemia and hypercapnia produce an increase of the pulmonary artery pressure through vasoconstriction. With persistent hypoxemia, polycythemia develops, increasing the blood viscosity and further impairing the efficiency of the cardiac muscle. When the right ventricle can no longer compensate for the increased work load, the end-diastolic pressure in the right ventricle increases, venous pressure increases, and right heart failure develops. Cor pulmonale implies right ventricular dilatation, hypertrophy, or failure secondary to chronic pulmonary disease; the presence of cor pulmonale implies a severe degree of chronic respiratory disease.

The association of hypoxemia, polycythemia, and cor pulmonale is encountered more commonly in patients with chronic obstructive pulmonary disease with chronic bronchitis, the so-called "blue bloater." When congestive failure occurs in the emphysematous patient ("pink puffer"), it is usually a terminal event.

Digitalis, diuretics, and restriction of sodium intake are just as much indicated in the treatment of right ventricular failure as they are in left ventricular failure, and digitalis is effective in the treatment of patients with cor pulmonale and congestive failure. Digitalis must be used cautiously. (47) In the patient with cor pulmonale, an increase in heart rate reflects pulmonary as well as cardiac insufficiency. *The use of digitalis to control increased heart rate can result in overdosage.* Digitalis toxicity is common and may manifest itself by digitalis-induced atrial arrhythmias, especially atrial tachycardia with block. Isoproterenol has an action on the heart similar to that of epinephrine, and the dosage should always be cut in half when the patient is taking digitalis.

Many patients present with chronic obstructive pulmonary disease and chronic respiratory acidosis with a superimposed metabolic alkalosis associated with hypokalemia due to thiazide diuretics. Potassium chloride should be administered oral-

ly and electrolytes checked frequently while the patient is being digitalized. Severe respiratory acidosis treated with hyperventilation causes potassium to pass from the cell into the plasma; plasma levels may exceed 7 mEq/liter. The heart takes up potassium as the skeletal muscle releases it. During the precipitous decrease in hydrogen ion concentration with mechanical ventilation, the potassium flux in the cardiac muscle is reversed and ventricular arrhythmias can occur (48). Digitalis is contraindicated during this phase.

The final instruction is carried out in the emphysema clinic. Patient education is an important aspect of treatment. Prior to dismissal, each patient is made to understand the long-term nature of the program and the importance of being vigorous with the intensive medical regimen. Through this approach we improve ventilation, provide more efficient breathing, and increase exercise tolerance.

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TOXICOLOGY OF THE BARBITURATES

Sidney Kaye, MSc, PhD

Several billion doses of barbiturates are legally prescribed by the medical profession yearly in the United States alone (1). It is no wonder that these derivatives can be found in almost every home and that more people *attempt* suicide with overdosage than with any other single *drug* (2). Since the barbiturates comprise an important and very useful group of central nervous system depressants, we must learn to live with them.

Its first member (diethyl derivative of malonyl urea) was introduced by Emil Fisher in 1903 and was called barbital (Veronal). The next to be synthesized was phenobarbital (Luminal). In the following years many hundreds of new derivatives have been synthesized in the search for "peace and/or sleep" pills. Of these, there are about a dozen that are in common use; all are derivatives of malonyl urea and their names usually end in "al" (3). They have the following structural formula:

Generally as the R_1 and R_2 radicals increase in length (up to six carbons), the potency increases. Also the presence of a double bond or of sulfur will usually increase potency.

From the Institute of Legal Medicine, University of Puerto Rico School of Medicine, San Juan, P. R.

TABLE I: CHEMICAL COMPOSITION

Name	R_1	R_2
Barbital	ethyl	ethyl
Phenobarbital	ethyl	phenyl
Amobarbital	ethyl	isoamyl
Butisol	ethyl	I-methyl propyl
Pentobarbital	ethyl	I-methyl butyl
Dial	allyl	allyl
Secobarbital	allyl	I-methyl butyl
Pentothal*	ethyl	I-methyl butyl

* *Sulfur substitutes for oxygen to make thio-urea instead of urea.*

Because of the great popularity of the barbiturates for suicides and because of uncertainties (sometimes) in rapid diagnosis and treatment, the following is offered as a brief resumé of some of the properties, signs, symptoms, toxicity, duration of action, rapid presumptive identification and treatment of barbiturate poisoning.

Pharmacology and Toxicity

Synonyms: (Slang among the addicts): Sleeping pills, goof balls, yellow jacket (Nembutal); Red Devils (Seconal); Blue Heaven (Amytal).

Uses: Anti-convulsant, sub-hypnotic, sedation, hyptonic, pre-anesthetic (basal), anesthesia, "truth serum", use as antidote for convulsants.

Properties: White crystalline powder, odorless and bitter, slightly acid, insoluble

in cold water, or petroleum ether at 40-60° C (hence a good way to purify). Water soluble as the sodium salt; soluble in chloroform, ether or alcohol.

MLD: The minimum lethal dose for a 150 lb. man varies from about 1 to 7 g depending upon the derivative's potency. Short acting members (rapid onset) usually are more potent; longer acting members (slow onset) are usually less potent. For example, the MLD for secobarbital is 1 g; the MLD for phenobarbital is about 7 g (4).

Excellent antidote for strychnine, and other convulsants.

Disadvantages:

Hangover is possible

Oral dose is safest, IV to be given only by the specialist.

Easily crosses placental barrier.

Too easily obtained; widespread use for suicides.

No analgesia until near coma (not like aspirin or morphine).

Fast acting derivatives are contraindicated with liver damage.

TABLE II: PHARMACOLOGICAL PROPERTIES COMPARED

Barbiturate	Duration of Action	Elimination	Coma, or awakening-Blood Level	Action	Similar to other members
Phenobarbital (Luminal)	Long to 24 hrs.	Delayed up to 3-5 days (Kidney)	8 mg %	Delayed and sedation	Barbital, Mebaral
Amobarbital (Amytal)	Intermediate, approx. 10 hrs.	Kidney and liver	2 mg %	Moderately weak hypnotic	Dial, Neonal, Ipral, Butisol, Alurate, Delvinal
Pentobarbital (Nembutal)	Short, approx. 8 hrs.	Mostly liver	1,5 mg %	Hypnotic	Ortal, Sandoptal, Phanadorn
Secobarbital (Seconal)	Very short, approx. 6 hrs.	Rapid, liver	1,0 mg %	Hypnotic	
Thiopental (Pentothal)	Ultra short, approx. ½ hr.	Very rapid, fat storage and liver	0,8 mg %	Ultra short & ultra potent; anesthetic	Evipal, Surital, Brevital

3 mg %would be ambulatory for phenobarbital (5).
3 mg %owould be coma for amobarbital.
3 mg % would be coma or fatal for pentobarbital.
3 mg % would fatal for secobarbital.

Advantages of therapeutic use:

Sedation, depression, sleep (to any degree, by chosing the specific derivative and varying the dose to suit the state of mind of patient and environment).

Many in group to chose from.

Produces calmness, relieves tensions; and margin of safety is wide.

Sedation is about 1/3 hypnotic dose.

Possible addiction (compulsion to use; withdrawal symptoms).

Contraindicated for the very old or the very young.

Synergism with many other depressant drugs; even with fatal outcome.

Acute signs and symptoms:

Lethargy, depression, ataxia, sleep to deep coma, lowered body temperature, de-

pressed circulation, marked fall in blood pressure, oliguria, respiratory depression, decreased response of respiratory center to carbon dioxide (Cheyne-Stokes), anoxia, cyanosis, flaccidity of limbs, retention of urine, usually constriction of pupils (but dilatation of pupils may later occur), corneal and other reflexes may be absent, deep coma, shock, cold extremities and death due to respiratory arrest. Intoxication is frequently associated with marked cardiovascular depression or pneumonia.

TABLE III: EFFECTS OF BARBITURATES

Effect	Therapeutic Dose	Toxic Dose
Respiration	None	Decrease sensitivity of respiratory center to CO_2 (Cheyne-Stokes).
Circulation	None	Depresses circulation (central); also direct vessel depression (shock).
Smooth muscle	None	Depresses peristalsis of intestinal, uterine and urethral muscles.
Temperature	None	Depresses heat regulatory center, plus vascular dilatation.

Chronic signs and symptoms:

Skin rash, slurred speech, cyanosis, amnesia, anorexia, emotional instability, ataxia, constipation, may occur.

Remarks:

The barbiturate derivatives are powerful depressants. In the presence of any other depressants, their action is even more powerful; at least additive action. This is especially so with alcohols, morphine derivatives, reserpine and tranquilizers. Great precaution or avoidance of these combinations is urged so as not to produce a crisis by their synergistic action.

Identification

(1) *Rapid Detection and Estimation in Blood* (6):

Reagents:

1. Mercuric nitrate ($Hg(No_3)_2$) in pH 8 phosphate buffer.
   (a) 1 g $Hg(N0_3)_2$ and 0.2 ml $HN0_3$ and 50 ml H_20 (Saturated solution)
   (b) 0.15 M phosphate buffer (pH8) 95.5 ml of 0.15 M Na_2HP0_4 — 5.3 g/100 ml ($Na_2HP0_4.12H_20$) 5.5 ml of 0.15 M KH_2P0_4 — 2.0 g/100 ml (KH_2P0_4) Check with pH meter and adjust if necessary.
   (c) Add 2 ml of satured $Hg(N0_3)_2$ (Sol. a) to 100 ml of the pH 8 buffer (Sol. b). Filter if turbid. This is table at room temperature.
   (d) Standard secobarbital (1-10 mg/99 ml H_20 plus 1 ml 0.5 N NaOH.
2. Diphenyl carbazone.
   Add 100 mg of "S diphenyl carbazone" to 100 ml of chloroform. Allow to stand (age) for 2 to 3 days in a flask in a lighted room. Then store in a dark bottle in the refrigerator. Solution is now stable for many months.

Procedure:

1. 5 ml of chloroform plus 0.5 ml of blood is gently shaken for about 1 minute and then filtered through Whatman No. 31 paper into a test tube, completely wetting the paper.

2. To this chloroform filtrate add 0.5 ml of buffer (pH 8); shake and mix for 15 seconds and then filter through small filter paper (Whatman No. 31) into a small test tube.

3. Transfer 2.5 of filtrate into a 10 mm cuvette, add 0.5 ml of diphenylcarbazone; mix and then wait 2 minutes. Blank is light pink; barbiturates yield a darker pink-lilac.

4. Read in a spectrophotometer at 550 millimicrons with a reference blank containing 2.5 ml of chloroform and 0.5 of diphenylcarbazone.

5. Compare with each known standard for an approximation, since the color molar absorbity is not the same for each barbiturate derivative.

6. Hydantoins interfere; check reagents for contamination by substituting water for blood and follow through procedure. Resulting solution should have same reading as the blank.

7. Confirm if possible by ultra violet spectrophotometry and/or thin layer chromatography (7, 8, 9, 10, 11) for differentiation.

(2) *Presumptive Test (Koppanyi)* (12).

Transfer 50-100 ml of urine or stomach contents into a large separatory funnel and test with litmus paper. If alkaline, barely acidify (dropwise) with dilute sulfuric acid.

Add 2 X volume of ether (100-200 ml) and gently shake for several minutes. Allow the layers to stand for several minutes to effect a good separation. The barbiturate is in the ether. Discard the lower aqueous layer.

Pass the ether through filter paper to remove droplets of water; collect into a beaker or pyrex evaporating dish.

Note: Water inhibits the color production of test, so the ether now must be dry.

Carefully evaporate to dryness on a water bath. (Do not use an open flame or high heat). The residue must by dry. Dissolve residue in about 5 ml of methanol. If the residue is dirty brown it requires cleaning prior to testing. Add a pinch of activated decolorizing charcoal and stir with the methanol. Filter and collect the clear filtrate into a small container. Wash filter paper once with several ml of methanol and again collect filtrate. Gently evaporate total filtrate to about 1 ml volume.

Transfer a few drops to a white porcelain spot plate. Add 1 drop of cobalt acetate (1% in absolute methyl alcohol) and then 2 drops of isopropyl amine (5% in absolute methyl alcohol). A purple to lilac color is positive for a barbiturate derivative. Test is sensitive to about 0.050 mg.

Report as negative, trace, moderate or large amounts.

Note: Presence of water even in traces inhibit the color production. Cobalt acetate should be kept in a light resistant bottle, when the cobalt pink color is faded, renew the reagent.

To check efficacy of reagents and for quality control, parallel a negative blank (a drop of pure chloroform) and positive controls (standards of a known barbiturate) at the time of testing unknown. (To prepare a standard containing 1 mg/ml,

dissolve a 1½ grain capsule of a common barbiturate in a 100 ml of chloroform).

This test will be positive in urine even days later when the barbiturate is a long-acting one (phenobarbital); but will be positive for only a very short time with a short-acting barbiturate such as secobarbital.

Phenobarbital requires both cobalt acetate and isopropyl amine to give a color whereas the other barbiturates turn blue upon the addition of only cobalt acetate, which however, intensifies on the addition of isopropyl amine and turns it lilac. This can differentiate the phenobarbital from the others especially in tablets.

Other similar drugs may also give a color (Ureides, hydantoins, Bromural, and Doriden).

(3) *Identification in Urine and Tissue*:

Since urine is an excellent vehicle for most drugs, and since it is here where they usually are found in the greatest concentrations, look for the presence of crystals in the above test (2) extraction. Purification by solvents or microsublimation would yield typical structures to be microscopically studied and compared with known barbiturate crystals. Secobarbital is difficult to crystallize from tissue, but time and effort may yield some crystals. Barbiturates are insoluble in petroleum ether at 40-60° C; (Good way to get rid of fats and oils).

Melting point is an excellent confirmation for the identification of characteristic crystals (Table IV).

Treatment of Intoxication

Careful evaluation of all reflexes (tendon and corneal) should be done. This is an excellent guide as to the depth of depression. At all times adequate respiratory exchange must be maintained, keeping the airway open and preventing aspiration.

TABLE IV: MELTING POINT OF BARBITURATES

Trade Name	Chemical Name	Melting Point
Alurate sodium	Sodium allyl, isopropyl	140-142°C
Amytal	Iso amyl, ethyl	152-155°C
Barbital (veronal)	Di ethyl	188-191°C
Butisol	5 ethyl-5 (I methyl propyl)	168-170°C
Cyclopal	Cyclo pentenyl, allyl	140-143°C
Delvinal (vinbarbital)	5 ethyl, 5 (I methyl, I butyl)	162-163°C
Dial	Di allyl	171-173°C
Evipal	N methyl, cyclo hexanyl methyl	143-145°C
Ipral	Ethyl, isopropyl	200-203°C
Kutonal	Methyl, phenyl	200-223°C
Mebaral	5 phenyl, 5 ethyl-3 methyl	176°C
Neonal	Ethyl, butyl	127-130°C
Nostal (Noctal)	5-2 bromoally-5 isopropyl	177-179°C
Ortal	Hexyl, ethyl	122-125°C
Pentothal	Sodium 5 ethyl, 5 (I methyl butyl) thio	159-160°C
Nembutal (Pentobarbital)	Ethyl, (I methyl butyl)	127-130°C
Pernoston	5-2 bromoallyl-5 sec. butyl	130-133°C
Phenobarbital (luminal)	Phenyl, ethyl	173-174°C
Phanadorn	Cyclo hexenyl, ethyl	171-173°C
Sandoptal	Isobutyl, allyl	138-139°C
Seconal (Secobarbital)	5-allyl-5 (methyl-butyl)	100°C

Tracheostomy should be performed if indicated by excessive secretions and difficulty in maintaining a clear airway. Artificial respiration, or oxygen (if indicated), using endotracheal tube if airway is obstructed, may be necessary.

As much of the drug as possible should be removed as soon as possible by gastric lavage, taking every precaution to avoid aspiration. Emetics are avoided if patient is depressed. Saline cathartic ($MgSO_4$, 30 g) into the gastrointestinal tract may be used to further minimize absorption of drug.

Adequate circulatory activity is supported with 5% glucose in water and/or a vasopressor in dosage *just adequate* to maintain near normal blood pressure, as *needed.*

All reflexes, respiratory pattern, skin color and response to painful stimuli are evaluated at frequent intervals to guide further therapy.

Patient is placed on his side so as to minimize the danger of aspiration and he is turned at regular intervals to prevent hypostatic pneumonitis. Broad spectrum antibiotic may be used prophylactically. Lungs are inflated fully with room air at least once every three hours to diminish atelectasis.

Nutritional, water and electrolyte balance and body heat must be maintained. Catheterization may be necessary.

To combat respiratory difficulties, artificial respiration or oxygen therapy should be used. The use of Picrotoxin, Metrazol, Amphetamine or other strong analeptics is now believed to be ineffective and perhaps dangerous for patients in deep depression and unnecessary for the mild cases. Mild analeptics such as Emivan, megimide (Bemegride), or Ritalin may be used (if you must), to just maintain reflexes and just keep the EEG active. They should not be used in an attempt to awaken the patient.

Detailed nursing care is vital especially during the acute phase. Coma may persist for days with the long-acting barbiturates. Prognosis is good if you can prevent anoxia.

If the drug blood level is high and the drug is a long-acting barbiturate, then hemodialysis may be used to advantage. Hemodialysis may be effective to hasten the elimination of many toxic agents. Success has been reported for other long-acting depressants.

The above suggesions are for the markedly depressed. If, however, the depression or overdosage is mild, then treatment should also be "mild". If respiration is normal, color is good, and twitching and corneal reflexes are present, it may suffice to let the patient "sleep it off", carefully watching him to prevent aspiration and any possible later development of respiratory difficulties.

Summary

The barbiturates as a group are the *drugs* most frequently used in *attempted* suicide, both here and in the United States. This is because they are so easily available, and are found in most homes.

Writing a prescription for a large number of tablets at a time should be done with great hesitancy and caution, and only for good reasons.

Because of the popularity of barbiturates for suicides, accidental combined action (synergism) with other depressant drugs or alcohol, and because of uncertainties (sometimes) in rapid diagnosis and

management, we have prepared this brief resumé of some of their properties, signs, symptoms, toxicity, approximate minimum lethal dose, duration of action and treatment. Analeptic drugs are now believed to be ineffective and perhaps even dangerous, and should be used only with great caution, if at all. In general, it is better to provide physiologic support to vital functions rather than give stimulants or analeptics in an attempt to awaken the patient.

The classic Koppanyi rapid, simple, presumptive test has been included in detail for those that have a need to do it in an emergency. This is a good test and can be performed with minimal equipment, time or training.

The signs and symptoms, treatment, and management are generally similar to those of other related depressant drugs.

Resumen

Los barbitúricos como grupo son las *drogas* usualmente más usadas en *intentos* de suicidio, tanto aquí en Puerto Rico como en los Estados Unidos, debido a su fácil adquisición. Con frecuencia se encuentran en muchos hogares.

Los barbitúricos solamente deben recetarse en cantidades pequeñas. Debido a su popularidad entre los suicidas, a su posible combinación accidental con otras drogas depresivas o con alcohol (sinergismo), y debido también a ciertas dificultades en el diagnóstico rápido y tratamiento de las intoxicaciones por barbitúricos, es que ofrecemos esta información como un breve resumen sobre sus propiedades, toxicidad, dosis letal mínima, acción, síntomas y tratamiento.

Los síntomas y signos de la intoxicación barbitúrica son generalmente similares a los producidos por otras drogas depresivas. El tratamiento es también generalmente similar, tanto en lo sintomático como en el de sostenimiento.

Las drogas analépticas no son consideradas en la actualidad efectivas, y debido al peligro de su uso, deben usarse solamente en última instancia y con gran precaución. En general es preferible mantener las funciones vitales que prescribir estimulantes o analépticos en una tentativa por despertar al paciente.

La bien conocida prueba de "Koppanyi", la cual es rápida y sencilla, ha sido incluída en detalle para aquellos que tengan la necesidad de verificarla en caso de urgencia. Es una prueba buena y puede ser llevada a cabo en muy poco tiempo, con un mínimo de equipo y por personas con poca experiencia.

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HEPATOPATIAS EXPERIMENTALES POR TIOACETAMIDA

Perfil Funcional

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En el año 1945 (1) en el Departamento de Agricultura Subtropical de Orlando (Florida) se descubre que la considerable pérdida de frutos de naranja por la acción de los hongos verdes y azul, *Penicillum digitatum* y *Penicillum italicum,* que asciende a 32.9%, se reduce substancialmente a 1.7% sumergiendo la fruta por 2 a 5 segundos en un baño de tioacetamida al 5%.

Poco después se observan alteraciones hepáticas (2) en humanos que consumían grandes cantidades de jugo de naranja y se comprueba que el jugo está contaminado con tioacetamida.

Desde entonces se ha investigado ampliamente la patología hepática experimentando con tioacetamida.

El animal comunmente empleado ha sido la rata. Se obtiene en ella necrosis mortal, cirrosis o tumores hepáticos según sea la dosis y la duración del experimento (3, 4, 5 y 6). Uno de estos autores, Schwietzer (5), dice que la cirrosis obtenida con tioacetamida es la más análoga a la cirrosis humana que se ha conseguido experimentalmente.

Presentado en la Sexagésimaquinta Convención de la Asociación Médica de Puerto Rico, San Juan, Puerto Rico, noviembre 1967.

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Otro de ellos, Ammon (6) afirma que el hígado se pone espoloneado y tuberoso como en las cirrosis del ácido salicílico pero se diferencia de ellas en que las del ácido salicílico se acompaña de ascitis y en las de tioacetamida no ocurre esto. Un autor (6) ha usado el conejo como animal de experimentación.

Se ha usado también la experimentación con tioacetamida en trabajos de regeneración hepática siempre en ratas (7, 8 y 9). La tioacetamida también se ha utilizado en respetable número de investigaciones sobre la fisiopatología hepática, usando ratas. Estos trabajos están citados en otra publicación nuestra (10).

Nosotros hemos experimentado con tioacetamida utilizando perros. En el curso de la patología hemos investigado las variaciones en el perfil hepático de las pruebas más aceptadas para explorar la patología humana y la electroforesis en sangre y en el líquido ascítico. También hemos investigado las variaciones que experimentan los scanigramas con Rosa de Bengala- ^{131}I y ^{198}Au en las diversas etapas de la patología experimental.

Procedimiento

Hemos utilizado 15 perros mongroles cuyo peso variaba entre 35 y 45 libras. Se han dividido en 5 series de 3 animales cada una que se han ido utilizando imbricando los

animales sucesivamente en el tiempo que ha durado el experimento que ha sido en total para las 5 series, dos años.

Los animales han sido alimentados con dietas especiales para perros a base de carne de caballo preparadas por la industria. Se ha suplementado este alimento con residuos de comidas humanas que resultaron ser las más apetecidas.

Todos los animales se desparasitan y se inicia el experimento 15 días después de este tratamiento en aparente estado de excelente salud.

En estas condiciones se hacen a los animales los exámenes de control que incluyen:

Proteínas totales del suero, albúmina y globulinas, curva electroforética de proteínas séricas, turbidez al timol, transaminasa glutámica oxalacética, fosfatasa alcalina, bilirrubina, bromosulfaleina y scanigrafía: Rosa Bengal-^{131}I y ^{198} Au.

Después se inicia la administración de la tioacetamida (TAM) cuya dosis ha ido decreciendo en el curso del experimento, de acuerdo con la experiencia. Se inició en la primera serie con dosis de 25 mg de TAM Kg/día que es la dosis fijada por dos investigadores (3 y 5) que usaron ratas. Según estos autores con esas dosis se conservan los animales vivos hasta alcanzar la etapa tardía en que obtienen las cirrosis. En nuestra experiencia esta dosis es muy drástica para los perros y la reducimos en la 2da. y 3ra. serie de animales a 25 mg Kg/días alternos y en la 4ta. serie la reducimos más administrando a cada animal 500 mg en total dos veces por semana. En la 5ta. y última serie hemos reducido aún más y nos hemos limitado a dar 500 mg en total semanalmente.

Hacia los 21 a 29 días de iniciar el experimento se manifiesta en los 12 animales que sobrevivieron los signos de necrosis hepática descritos con detalle en otro trabajo nuestro (10). Las orinas eran ictéricas, daban la reacción de Millon positiva y contenían moderada cantidad de albúmina.

Se realizan las mismas pruebas de exploración en los 12 animales.

En los días sucesivos fallecen 6 animales en los que se comprueba la necrosis masiva del hígado (Fig. 1). Dos de ellos tenían ascitis.

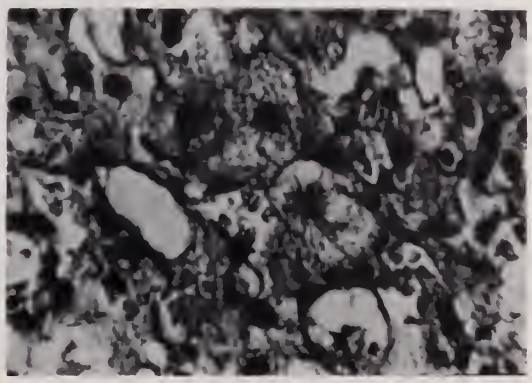


Fig. 1: Demuestra la desorganización de los cordones de células hepáticas y las diversas fases de la degeneración celular que ocurre. Muchos núcleos son monstrusos. X 750.

Los 6 animales restantes se mantienen en el experimento y pasados los 3 meses todos ellos demuestran ascitis. Se realizan en los 6 animales las exploraciones indicadas (Figs. 2 y 3).

Tres de los animales fallecieron antes de llegar a los 4½ meses. Se comprueba en los 3 ascitis y cirrosis hipertrófica con superficie de granulación fina.

Sobrevivieron los 3 restantes animales hasta pasado seis meses. Se realizan en ellos las mismas exploraciones. Uno de los animales falleció de hemorragia gastro-intestinal a los pocos días y los restantes dos, se sacrificaron.



Fig. 2: Cirrosis hipertrófica. Superficie con dibujo de granulación fina.

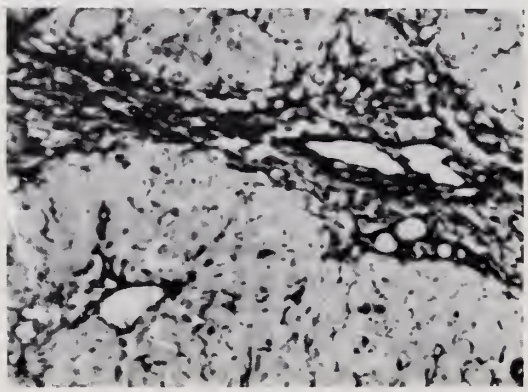


Fig. 3: Cirrosis hipertrótica. Coloración del retículo en un caso de cirrosis precoz. X 300.

Estos tres animales tenían abundante ascitis y un hígado pequeño con superficie de nódulos irregulares. Al microscopio mostraban cirrosis tipo Laënnec (Figs. 4 y 5).

Resultados

Los resultados están resumidos en la Gráfica 1. En cada caso el resultado que se refleja se ha compuesto con la media aritmética de todos los animales del grupo.

En el análisis de las curvas observamos que exceptuando la B S P y las curvas electroforéticas del suero, los restantes metabolitos explorados dan valores en cifras dentro de los límites que se consideran normales para los humanos.

En las curvas electroforéticas de los controles se observan un aumento de las globulinas γ, β en relación con las curvas normales de los humanos.

Ninguno de nuestros 15 perros retiene trazas de la B S P explorada con la técnica de 5mg Kg/45. Thomson (11) et al experimentando con perros y estudiando la literatura sobre el tema afirman que la B S P es captada rápidamente de la circulación sanguínea por el hígado normal de los perros.

Al llegar a la etapa de necrosis hepática todas las pruebas se desvían de los límites normales. El cociente albumino-globulina se desvía bajando la albumina a 2.97g y subiendo las globulinas a 4.50 g. Todos los perros muestran ictericia siendo el valor medio total de la bilirrubina 4.2 mg%. La turbidez al timol es la reacción que menos se afecta en todos los estados patológicos. Por el contrario la B.S.P. resulta la prueba más sensible puesto que de no retenerse nada en los controles, se eleva la retención en la necrosis hasta 42% como cifra media.

El aumento de la fosfatasa alcalina también es notable en la necrosis. La S.G.O.T. se eleva moderadamente en el período de la necrosis en que se tomaron las muestras.

Los animales que llegaron al estado de cirrosis hipertrófica mantienen la desviación albumina-globulinas, desaparece la hiperbilirrubinemia, disminuye la retención de B S P a 10%, disminuye considerablemente la fosfatasa alcalina y la S.G.O.T. retorna cerca de los valores normales.

Los tres animales con cirrosis de Laënnec: reflejan muy marcadamente la altera-



Fig. 4: Cirrosis nodular atrófica a los 6½ meses.

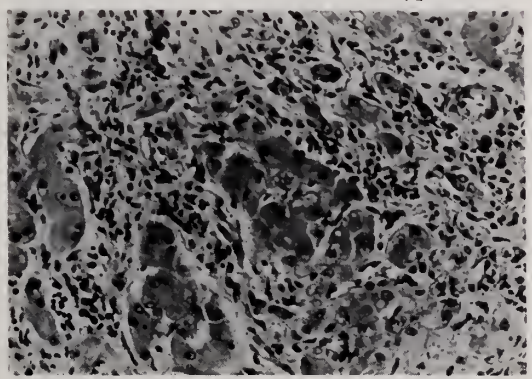
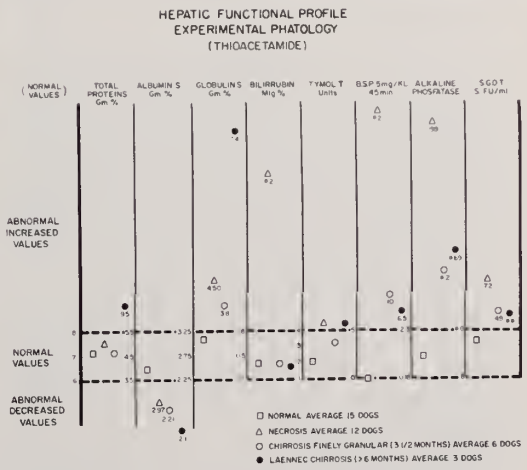
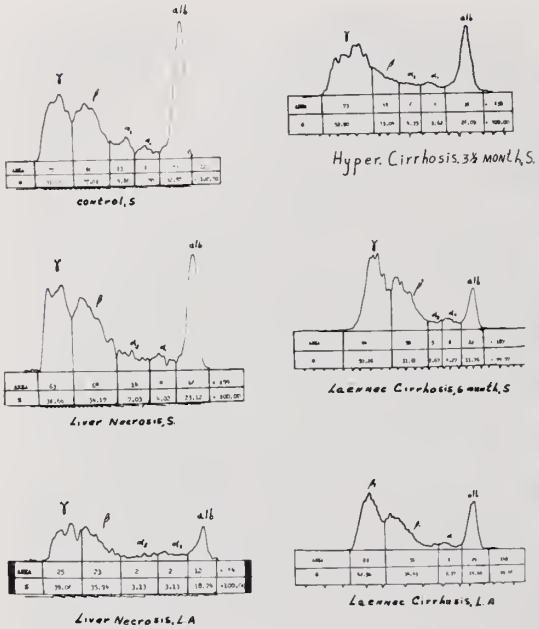


Fig. 5: Cirrosis portal bien establecida en perro sacrificado a los 6½ meses. X 250.



Gráfica 1: Las curvas del perfil funcional hepático durante el curso del experimento.

ción de las fracciones proteínicas de la sangre. Una baja de la albumina a 2. 1g% con enorme elevación de las globulinas a 7.4g %. Exceptuando ligera elevación de la fosfatasa alcalina los otros metabolitos explorados en este grupo de 3 cirrosis tipo Lae-



Gráfica 2: Las curvas de electroforesis en el suero (S) y líquido ascítico (L.A.) en el curso del experimento.

nnec están cercanas a los límites normales.

Electroforesis

En nuestras curvas se ve que la elevación de las globulinas en las necrosis se hace a expensas de las globulinas γ, β en tanto que en los dos grupos de cirrosis la elevación predominante es de la globulina. En la cirrosis tipo Laennec la hipertrofia de la globulina y la disminución de la albumina son marcadísima (Fig. 6).

La electroforesis de los líquidos ascíticos tanto en las necrosis cuando las hubo, como en las cirrosis siguen en un nivel mucho menor la misma proporción de las curvas de los sueros.

Escanigrafías

Las lesiones hepáticas de carácter difuso que se producen en nuestros perros quedaron bien demostradas desde muy precozmente por la creciente incapacidad del parenquima hepático para captar el Rosa de Bengala-^{131}I, en tanto que se mantuvo la capacidad del retículo endotelio de fijar el oro coloidal-^{198}Au. Hay una total disparidad entre los trazados hipocaptantes o fríos del Rosa de Bengala-^{131}I y los trazados activos obtenidos con oro coloidal-^{198}Au (Figs. 7 y 8).

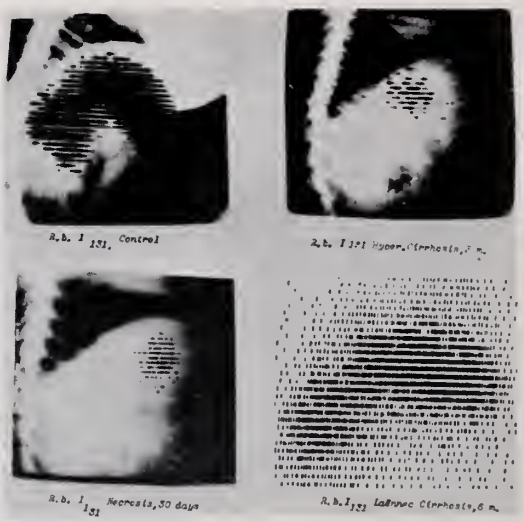


Fig. 6: Scanigrafía con Rosa de Bengala—^{131}I, en las diferentes etapas del experimento.

Comentarios

Las alteraciones más precoces y más persistentes en el perfil funcional se establecen en las proteínas de suero. La precoz y marcada disminución de la albumina se explica por una investigación de Barker y colaboradores (12). Estos autores comprueban la precoz disminución de la incorporación de aminoácidos a las proteínas del hígado y subsiguiente disminución de la seroalbumina producida por este órgano en ratas intoxicadas con tioacetamida. En el curso del experimento se acentúa la disminución de albumina elevándose simultáneamente la globulina en la fase de la necrosis. En la

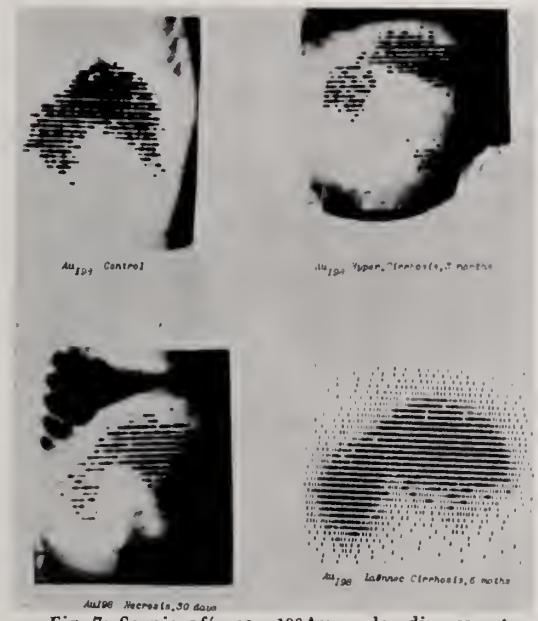


Fig. 7: Scanigrafía con ^{198}Au en las diversas etapas del experimento.

cirrosis avanzada post-necrótica y nodular de tipo Laennec, nuestras curvas electroforéticas reproducen la señalada por Menéndez-Corrada y colaboradores (13) para la cirrosis de hígado post-necrótica de humanos. Hay una disminución muy marcada de la curva de albumina y una elevación extraordinaria de las globulinas.

La cifra media de S.G.O.T. en nuestros animales con necrosis, es baja considerando las que se encuentran en los humanos. Estudios experimentales de Ress y Sinka (14) y los de Varga y Molnar (15) demuestran que la elevación de la S.G.O.T. en el suero es un signo precoz de la necrosis hepática coincidiendo con la lesión de las mitocondrias que es la más precoz. En nuestros casos las cifras más bajas de la S.G.O.T. la dieron los 6 animales que fallecieron a los pocos días. Por el contrario, en las necrosis menos severa hemos encontrado cifras de 194 y 176 unidades.

La ictericia con elevación de la bilirrubina es un signo constante de la necrosis. Desaparece en el estadio de las cirrosis.

Otro signo que también caracteriza la necrosis es la retención de B.S.P que tiene gran valor diagnóstico en estos animales que normalmente poseen tanto poder de captación del colorante. Al llegar al estadio de la cirrosis el hígado recupera la captación y la BSP se acerca a la cifra normal de los humanos.

En nuestros estudios han resultado signos característicos de la necrosis, la retención BSP, el aumento S.G.O.T., la hiperbilirrubinemia, la incapacidad de captación del Rosa Bengala-^{131}I y la inversión albumina/globulina.

La cirrosis se caracteriza fundamentalmente por la hipertrofia de las globulinas y por la extrema disminución de la sero albumina, asi como la persistencia de pobre captación de la Rosa Bengala-^{131}I. Los animales recuperan la plena captación del ^{198}Au.

Resumen

Se ha experimentado con tioacetamida en perros. Hacia los 20-30 días se produce necrosis hepáticas. Los que sobreviven los primeros 3 meses desarrollan cirrosis tipo hipertrófico con granulaciones finas en la superficie hepática. Los que sobreviven más de 6 meses tienen cirrosis tipo Laennec con superficie nodular irregular.

En la etapa de la necrosis se perturban casi todas las pruebas siendo las más fielmente perturbadas: la BSP, la elevación de la bilirrubina, la S.G.O.T. como reacción precoz, la elevación de la γ,β globulinas con disminución de la albumina sérica.

El hígado pierde casi por completo la capacidad de captación de la Rosa Ben-

gala-^{131}I y disminuye manifiestamente la capacidad de captación del ^{198}Au.

En la cirrosis la desviación albumina/globulina se exagera con disminución de la albumina a valores cercanos a 2% y elevación considerable de las globulinas fundamentalmente por el aumento de la globulina.

Subsiste la pobre captación de la Rosa Bengala-^{131}I y se recupera el poder de captación del ^{198}Au.

Agradecimiento

A la señora Rivera de Sala y a la Dra. M. Cancio del Medical Research Laboratory, Veterans Administration Hospital, por las determinaciones electroforéticas de los sueros y líquidos ascíticos, y al Servicio de Cirugía Experimental del Centro Médico, P. R. School of Medicine por procurarnos los animales utilizados.

Summary

Thioacetamide has been employed experimentally in dogs, in which hepatic necrosis has been induced within a period of 3 to 4 weeks. The animals that survived over a 3 months period but less than 6 months, eventually came up with a type of hypertrophic cirrhosis characterized by fine surface granularity; whereas, those surviving over 6 months developed a Laennec like type of cirrhosis with nodular and irregular surface.

During the phase of necrosis, liver biochemistry is profoundly disturbed; this is very neatly shown by alterations of the BSP, hyperbilirrubinemia, early detection of changes in SGOT, market hyperglobulinemia in association with hypoalbuminemia.

The liver loses virtually its capacity for uptake of ^{131}I rose bengal and that for colloidal gold (^{198}Au) is sensibly diminished. In the cirrhotic stage the reversal of the albumin-globulin ratio is greatly exaggerated by a steep decrease of serum albumin down to a 2% level and by a marked rise of serum globulin levels which is largely due to an increase of gamma globulin.

Persistent liver cell damage was indicated by serial demostration of poor uptake of ^{131}I rose bengal in the cirrhotic animals.

Recovery of reticulo-endothelial function was shown by good uptake of radioactive colloidal gold.

Serial demostration of poor uptake of ^{131}I rose bengal indicated persistence of liver cell damage, whereas good uptake of colloidal gold (^{198}Au) demostrated recovery of reticuloendothelial function.

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RETICULOENDOTHELIOSIS WITH BLUE-STAINING GRANULES

A Disease Resembling Niemann-Pick's With Sjogren's Syndrome

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A. Barquet-Chediak, MD

A condition resembling Niemann-Pick's disease was first described in two adults by Sawitsky, Hyman and Hyman (1) in 1954. One was a 34-year old Puerto Rican female, the other a male of Italian origin. The condition was characterized by hepatosplenomegaly and by cells resembling those seen in Niemann-Pick's in the bone marrow and spleen. These histiocytes were described as different from those of Niemann-Pick's because of a blue granulation on the cytoplasm when studied with Wright's stain. Histochemical studies revealed that the cells were PAS positive, not digested by diastase, did not show metachoromatic staining with toluidine blue, had a negative alkaline phosphatase and showed a negative Sudan III reaction.

In 1961 Malini (2), and in 1964 Cogan and Federman (3) reported two additional cases. The following year Silverstein (4) and later on Thompson and Moloney (5) reported two cases elevating the total to date to six.

Our case is the seventh of this condition so far described. Ours had the additional features of rheumatoid arthritis and keratoconjunctivitis sicca (Sjogren's syndrome) making it the first case in the literature with both conditions occuring together.

From the Department of Medicine, San Juan City Hospital, and the Hematology Department, Puerto Rico Medical Center. and the Department of Pathology, School of Medicine of P. R.

Case Report

A 24-year old white woman entered the San Juan City Hospital because of bilateral flank pain, fever, chills and dysuria of five days duration. She had been feeling well for the past few months except for blurred vision and a sandy feeling in her eyes. Further questioning disclosed that she had been suffering from rheumatism since the age of 12 years with residual limitation of motion of the hands and wrists. She was gravida I, para I, and as far as she knew her parents were alive and doing well.

Physical examination disclosed a well developed, undernourished, acutely ill female. She was well oriented and appeared to be of fairly normal intelligence. Temperature was 39.4°C., pulse 120/minute, B. P. 110/70 mm Hg. Fundoscopic examination was not adequate because of hazy corneae. The chest was clear. The heart revealed no enlargement but a grade II systolic murmur at the apex and a sinus tachycardia were detected. Examination of the abdomen showed tenderness of both flanks. The liver was enlarged to 12 cm below the xyphoid process and the spleen 8 cm below the left costal margin at the anterior axillary line firm, smooth and non-

tender. Examination of the upper extremities showed mild ulnar deviation of the phalanges, limitation of motion at both wrists with synovial thickening of same, and a subcutaneous nodule at the right elbow.

Studies in the hospital revealed the following: Hemoglobin was 7.3 g; white blood cell count 2,300 with a differential of 4 stabs, 42 segmented and 54 lymphocytes. The urine was loaded with pus cells. Platelet count was 206,000; L.E. cell preparation negative; antinuclear antibodies negative; serum protein electrophoresis: albumin 33.79%; alpha 1 globulin, 3.38%; $alpha_2$ globulin, 8.11%; beta globulin, 7.43%; gamma globulin, 47.29%; BUN 19 mg%; SGOT, 12 units; SGPT, 10 units; serum uric acid, 3.25 mg%; total cholesterol 87 mg%. LDH, 620 units; latex fixation test negative; blood sugar 90 mg%. Examination of the bone marrow disclosed giant vacuolated histiocytes with blue spots in the cytoplasm. (Figures 1, 4) Examination of splenic aspiration again yielded similar cells. Histochemical study showed them to be PAS positive (Fig. 2) red oil "O" positive (figure 3), Sudan III positive, peroxidase negative, alkaline phosphatase negative, toluidine blue orthochromatic iron negative and Sudan IV positive.

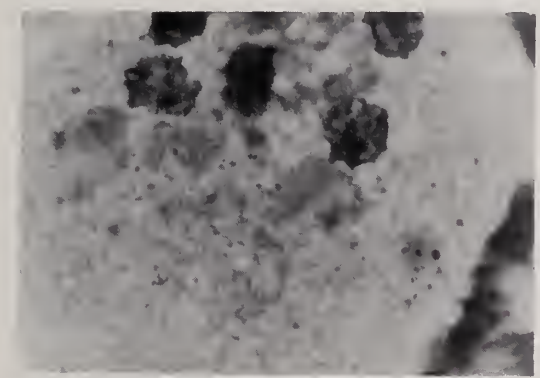


Fig. 1: Bone marrow smear showing reticuloendothelial cell with large blue inclusions (Wright's stain).



Fig. 2: Smear from spleen shows PAS positive granules in reticuloendothelial cell.

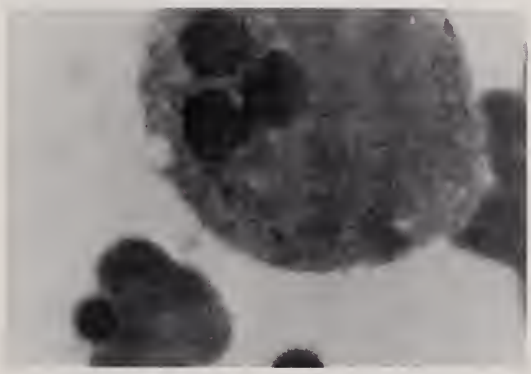


Fig. 3: Spleen. Sudan IV stain is positive.

Biopsy of the nodule in the right elbow was found to be compatible with rheumatoid granuloma. X-rays of the hands disclosed changes compatible with a rheuma-

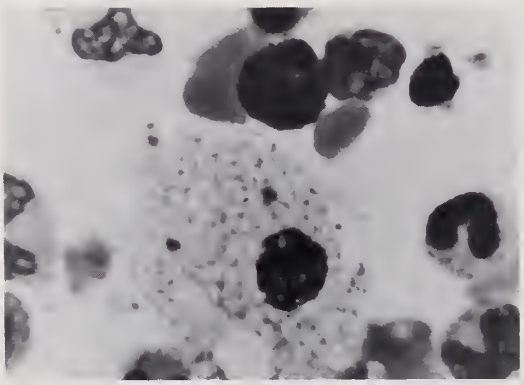


Fig. 4: **Spleen. Prussian blue stain for iron is negative.**

toid process. Opthalmologic consultation revealed no cherry red spot, but instead there were changes in the cornea and conjunctive, plus an abnormal Schirmer test confirmatory of keratoconjunctivitis sicca. A biopsy of the lacrimal gland done to rule out invasion by the abnormal histiocytes, revealed atrophic changes. Several sputum and urine sample studied for Niemann Pick's cells were negative. Barium swallow was negative for esophageal varices.

The patient's three-year old girl seemed well developed for her age and showed no hepatosplenomegaly. No studies were done of peripheral blood or bone marrow searching for signs of the lipid storage abnormality. Final diagnoses were acute pyelonephritis, Sjogren's syndrome and adult Niemann-Pick-like disease.

Discussion

The most common lipid metabolic disorders are shown in Table I schematically.

TABLE I: DISORDERS OF LIPID METABOLISM

TYPE	Predominant Substance Stored		
	Ganglion cells	RES cells	Parenchmal cell of viscera
I- Disorders in blood lipids			
A- High blood lipids			
1- Essential hypercholesterolemia	None	None	None
2- Essential hypertriglyceridemia	None	None	None
B- Low lipids in blood			Excess triglyceride in mucosal
1- Acanthocytosis (6)	None	None	cell of small intestine
2- Tangiers disease (7)	None	Cholesterol esters	None
II- Disorders of intracelular lipid metabolism			
A- Primary			
1- Phospholipid lipoidoses			
a- Nieman-Pick (8)	Sphyngomyelin	Sphyngomyelin	Sphyngomgelín
b- Cephalin lipidoses (9)	Nosamine phosphatide	Nosamine phosphatide	None
2- Glycolipid lipidoses			
a- Tay-Sacs and variants (10)	Ganglioside	None	None
b- Gaucher's (11)	Kerasin	Kerasin	Kerasin
c- Metachromatic leukoence-phalodystrophy (12) (13)	Sulfated glycolipid	Sulfated glycolipid inglia of CNS	Sulfated glycolipid in kidney and liver
3- Other			
a- Ceroid storage disease (14)	None	Ceroid	None
b- Lipid dermatoarthritis (15)	None	Glycolipid	None
c- Lipoid proteinosis (16)	Extracellular glycolipoprotein in skin and mucous membranes		
B- Secondary (symptomatic)			
1- Hans-Schüller-Christian (17)	Cholesterol	Cholesterol	Cholesterol
2- Saltztein series (18)	None	Lipid containing histiocytes in spleen	None
3- Hill series (19)	None	Lipid contains from cells	None
4- Sundberg series (20)	None	Blue pigmented macrophages	None

Detailed discussion of each entity is out of the scope of this paper. The reader is referred to the references for good reviews in the subjects (6-20).

Niemann-Picks disease in children is a rare familiar disorder characterized by sphingomyelin and other lipid accumulation in the reticuloendothelial cells throughout the body. Hepatosplenomegaly and retarded nervous and physical development are usually observed within the first six months. Death usually occurs by the age of one to three years.

Dusendschon (21) and Pflandler (22) were the first to report the adult type of Niemann-Pick's disease in 1946.

Terry et al (23) described a fatal case in a middle aged male that appeared to be Niemann-Pick's by appearance of the cells, but chemical analysis of the organs showed lower concentration of sphingomyelin than that previously reported in this disease; however, there were other lipids in larger amounts than those expected in this entity. Thus, they believed it to be a new type of lipoidosis.

Baar and Hickmans (9) reported a new disorder of lipid metabolism in children characterized by increased deposits of cephalin.

Landing and Shirkey (14) reported a new syndrome of lipoidosis characterized by brownish stained pigmentation, and found it to be due to ceroid deposition. It was also different from Niemann-Pick's when studied by histochemistry.

Saltzstein, (18), in a series of seven patients undergoing splenectomy for thrombocytopenic purpura (ITP) noted a marked accumulation of lipid-containing histiocytes in the spleen. Imprint smears from the spleen, stained with Wright or Giemsa, were not described in his report and in none of these cases were typical blue pigmented histiocytes noted in bone marrow preparations. Marshall (25) did not find the blue pigmented histiocytes in his case similar to Saltzstein's case, either.

Hill *et al* (19), using electron microscopy, studied foam cells in the spleen, bone marrow and lymph nodes of patients with various blood dyscrasias. Foam cells were found chiefly in spleens and other tissues of patients with ITP and a few other conditions associated with increased destruction of platelets and other blood elements. Typical foam cells were found in fourteen cases of thrombocytopenia, six patients with acute leukemia, a case of hypoplastic anemia and a patient with Felty's syndrome. The appearance of these cells in fresh smears or imprints stained with Wright or Giemsa was not described, but they were not so crowded as in our case. Hill *et al* postulated that the therapeutic use of corticosteroids played a role in the development of the storage cell phenomenon.

In 1964 Sundberg (20) and her coworkers reported blue pigmented macrophages in chronic myelogenous leukemia, in Stockholm. However, while the cytoplasm stained a blue-green color with Wright or Giemsa, the material appeared homogenous or somewhat striated and lacked the typical granular appearance of histiocytes found in marrow and splenic smears of this type of disease.

Only six cases of the so-called histiocytosis with blue staining granules have been reported so far (Table II). Our case increases the total to seven. It is of interest that two of them are Puerto Ricans. No known family relationship between these

TABLE II: CLINICAL AND LABORATORY DATA ON SEVEN CASES OF LIPID STORAGE DISEASE

Authors and Year	Age Sex	Enlarged Spleen	Enlarged Liver	Other Clinical and Laboratory Features	Cytologic Examination of Organs BM	Spleen	Liver	Other
Sawitsky, Hyman and Hyman, 1954	34 F	Yes	Yes	Asymptomatic-mild purpura	Smears showed storage cells	Not examined	Biopsy- no storage cells	
As above	26 M	Yes	Yes	Moderately severe purpura, 20 years' duration	Smears showed storage cells	Imprint smears and sections Showed storage cells	Biopsy- no storage cells	
Malinin, 1961	30 F	Yes	Yes	Asymptomatic	Smears showed storage cells	Not studied	Biopsy-storage cells in sinusoids and periportal connective tissue	Storage cells in mesenteric lymph nodes
Cogan and Federman, 1964	24 F	Yes	Yes	Mild anemia and thrombocytopenia: granular lesion of fovea; splenectomy	Smears showed storage cells	Storage cells in smears and sections	Not studied	
Silverstein, Young, Remine and Pease, 1964	60 F	Yes	No	Gall stones, post-necrotic cirrhosis splenectomy	Smears and section showed storage cells	Angiomata storage cells in section	Biopsy-post necrotic cirrhosis; no storage cells	Storage cells in mesenteric lymph nodes
Thompson and Moloney, 1965	34 F	Yes	No	Thrombocytopenia slight	Smears showed storage cells	Aspiration Smears showed storage cells	Not studied	
Román and Barquet	24 F	Yes	Yes	Leukopenia, anemia Sjogren's syndrome	smears showed storage cells	Aspiration smears showed storage cells	Not studied	

two cases has been established. Of the total of seven, six are females. Table III has been modified from Thompson and Maloney (5). It may be observed in it that there is some heterogeneity in the staining properties of the abnormal macrophages. Table IV shows the expected results of histochemistry in the most common storage diseases.

Some authors have classified this condition as different from Niemann-Pick's because of the large blue inclusions in the cytoplasm and its benignity as compared to its malignancy in the childhood counterpart. Also, one case (4) was found to have increased amounts of mucopolysaccharides in the urine, and another, on postmortem examination of the visceral lipids, was found to have smaller concentrations of sphyngomyelin when compared to the other lipids.

The hypocholesterolemia in our patient is difficult to explain. There was not chemical or clinical evidence of severe liver disease, nor the characteristics features of Tangier disease or sprue.

The simultaneous presence of Sjogren's syndrome and adult Niemann-Pick like disease in our patient can be only explaned on the basis of coincidence. This is the first such case reported in the literature. We found no basis for attributing the lachrymal gland atrophy or the joint involvement to infiltration by the abnormal

TABLE III: LIPID STORAGE DISEASE: HISTOCHEMICAL AND BIOCHEMICAL STUDIES

Authors & Year	Wright and Giemsa Stains	PAS	Sudan Black B	Toluidine Blue	LAP	Other	Results of Biochemical Studies	Comment Storage Material
Sawitsky Hyman & Hyman, 1954	Large reticuloendothelial cells, packed with blue staining granules, foamy reticuloendothelial cells	Pos.	Neg.	Neg.	Neg.		None	Mucopolysaccharides
As above	As above	Pos.	Neg.	Neg.	Neg.		None	As above
Malinin, 1961	Large reticuloendothelial cells, blue staining granules-macrophages	Pos.	Pos. (after harsh treatment)	Pos.	Not done	H & E granules did not stain	None	Bound fat of fatty acid
Cogan & Federman, 1964	Large storage cells, 15 to 80 u also foam cells- histiocytes	Pos.	Pos.	Not done	Not done	Birefringence pos.	Great increase in total lipid, phospholipid and sphingomyelin of spleen	Storage material similar to Niemann-Pick's
Silverstein, Young, ReMine and Pease, 1964 Thompson,	Histiocytes with blue staining granules Histiocytes with	Pos.	Pos.	Neg.	Neg.	H & E granules did not stain	Sialic acid chromatography-increased sphingomyelin and cerebro-sides of spleen	Glycolipid or phospholipid or both, excretion of urinary acidmucopolysaccharide
& Moloney, 1965	blue granules, vacuolated looking macrophages	Pos.	Neg.	Neg.	Neg.	Birefringence pos., VPO neg., esterase-neg.	None	Lipid storage disease
Román & Barquet	Histiocytes with blue granules, vacuolated looking macrophages	Pos.	Not done	Neg.	Neg.	Peroxidose-neg. Red oil O-pos. Sudan III-pos. Sudan IV-pos.	None	Similar to Niemann-Pick's

TABLE IV: EXPECTED RESULTS WITH HISTOCHEMISTRY (24)

Stain	Significance	Adult Gaucher's Disease	Cephalin-Lipidosis	Niemann-Pick Disease
Periodic acid-Schiff	Glycolipids dark red	Strong Pos.	Strong Pos.	Weak pos. to neg.
Metachromasia (1% toluidine blue)	Sulfuric, phosphoric, or carboxil esters of sugars & phosphoryl group of phospholipid change color of blue dye toward red	Neg.	Neg.	Pos.
Iron (Prussian blue reaction on paraffin sections)	Ferric iron stains blue	—	—	Neg.
Oil red (in propylene glycol)	Oil-soluble fat stain (propylene glycol as solvent increases staining of phospholipid	Not reported but would expect similar results to Sudan IV except for more intense staining of phospholipid-containing cells.		
Sudan IV (in acetone- alcohol) Hydrolyzed Nile blue sulfate (1% in water) Schultz cholesterol	Oil-soluble fat stain. Stains neutral fats red to pink and other lipids. Blue Cholesterol, its esters, and carotene stain blue-green.	Neg. Blue Neg.	Pos. — —	Pos. Purple to blue Pos.

macrophages. Even though similar cells have been described in Felty's syndrome, the severity of the infiltration plus the histochemical characteristics of our patient's cell point against the diagnosis of Felty's syndrome.

Summary

The seventh case of a storage disorder of unknown etiology is described, with cytochemistry studies. No hereditary or significant etiologic factors were discovered. Of the seven cases, two were Puerto Ricans. The disease is characterized by a benign course, splenomegaly and in some cases thrombocytopenia. A lipid - containing histiocyte with unique blue-staining granular cytoplasm was present in bone marrow and splenic smears. Concominantly the patient had a Sjogren's syndrome.

Resumen

En 1954 Sawitzky, Hyman y Hyman reportan por primera vez una nueva tesaurismosis, en una mujer puertorriqueña y en un hombre de descendencia italiana.

Esta nueva forma de tesaurismosis, se caracteriza por hepato — esplenomegalia y la presencia en médula ósea y en el bazo de unos macrófagos cargados de un pigmento azul cuando se colorea con Wright. — Además, las coloraciones de citoquímica muestran que estas células son P.A.S. positivas, no muestran cambios metacromáticos con azul de toloidina, son fosfatasa alcalina negativa, no dan coloración de hierro y el Sudan III es variable.

Posteriormente se han reportado cuatro casos más en la literatura mundial. Nosotros presentamos un nuevo caso lo que eleva el total a siete, de los cuales dos son puertorriqueños.

En nuestro caso se trata de una mujer de 24 años que ingresa por una pielonefritis y entre los hallazgos físicos, se encuentra una esplenomegalia, un síndrome de Sjógren's y se demuestran la presencia de los macrófagos azules en la médula y en el bazo y se confirman con las pruebas de citoquímica.

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EFFECT OF TRIAMCINOLONE ADMINISTERED EVERY OTHER DAY ON PITUITARY AND ADRENAL FUNCTION

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In 1949 Dr. Phillip Hench and the group from Mayo Clinic (1) first reported on the dramatic response of patients with rheumatic diseases to the administration of cortisone. At the time it was thought that the problem of therapy in this group of illnesses had been solved. Soon afterwards, it was realized, that the drug used had many undesirable side effects and that suppression of adrenal function was induced. New synthetic steroids were developed in the search for a substance that would have the same therapeutic efficacy without side effects. However, it rapidly became evident that adrenal-pituitary suppression always occured with the use of these substances in a daily dosage schedule.

Because of these effects different dosage schedules have been tried. In 1951 Lange (2) suggested that corticosteroids administered in an intermittent dosage schedule might be effective and in 1958 he (3) published his results with this form of therapy in a group of patients with the nephrotic syndrome. In 1960 Reichling (4), making use of the concept first suggested by Menkin (5) that substances in the blood stream tend to concentrate at inflamed sites and become fixed, treated a number of patients with a diversity of diseases with triamcinolone in a single dose every other day. In 1963, Harter, Reddy and Thorn (6) reported on the effect of this form of therapy on adrenal function. In 1964 Fisher (7) reported on the effect on adrenal-pituitary function of a 7 days on — 5 days off schedule of triamcinolone in a group of patients with juvenile rheumatoid arthritis. They all reported good response to this form of therapy in a fairly high percentage of patients and a marked reduction in the incidence of side effects.

It is our purpose to report our findings with the use of triamcinolone* on an alternate day single dose schedule in a small group of patients with connective tissue diseases, specifically in relation to the effect of this form of therapy on the adrenal pituitary axis.

Material and Methods

To date we have studied 10 patients with connective tissue diseases that include 4 patients with rheumatoid arthritis, 5 patients with systemic lupus erythematosus and 1 patient with dermatomysitis and arthritis (Table I). Of these, 1 patient had

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This study is supported by a grant from Lederle Laboratories, a Division of American Cynamid Company, Pearl River, N.Y.

Presented in part at the Regional Meeting of the American College of Physicians, San Juan, Puerto Rico, November, 1966.

* *Supplied as Aristocort by Dr. José A. de Jesús, Lederle Laboratories*

TABLE I: MATERIAL STUDIED

Case No:	Age (Years)	Sex	Diagnosis	Associated Diseases
1	30	F	RA•	
2	69	F	RA	Diabetes mellitus
3	29	M	RA	Hypercortisonism?
4	66	F	RA	Aortic insufficiency
5	19	M	DM•	Osteochondritis
6	30	F	SLE•	
7	37	F	SLE	Polymyositis
8	16	F	SLE	
9	27	F	SLE	
10	18	M	SLE	

RA=rheumatoid arthritis; DM=dermatomyositis; SLE =systemic lupus erythematosus.

received corticosteroids a year previously, 1 had been receiving prednisone for 5 months up to the day of admission, another had received prednisone 4 years previously which was discontinued because she developed diabetes mellitus, and 7 patients had never received steroid therapy.

All patients were admitted to the hospital, all medications were discontinued, and necessary studies to establish a diagnosis were performed. Besides, because these patients were to receive corticosteroids, the following additional studies were done: tuberculin test (P.P.D. intermediate strength), glucose tolerance tests (G.T.T.), chest X-ray, and if indicated, gastrointestinal series, serum electrolytes, radioisotope renogram, renal biopsy, and other renal function studies.

The pituitary and adrenal functional status was investigated as follows. A control 24 hour urine collection was done on the third hospital day for determination of 17 ketosteroids and 17 hydroxycortico-steroids, by the method of Drekter (8) and Silber and Porter (9) respectively. Normal values in our laboratory are 5 to 20 mg for 17 ketosteroids and 3 to 12 mg for 17 hydroxycorticosteroids in a 24 hour period. Creatinine determination was done to establish the adequacy of the collection. A Metyrapone® test was performed using the original method of Liddle (10) on the fourth and fifth hospital day. The normal response to the administration of Metyrapone, 750 mg every 4 hours for 6 doses, should be at least a twofold increase in the control determination of the 24 hour urine hydroxycorticosteroids occuring either on that same 24 hour period or on the subsequent day. On the sixth and seventh days an ACTH adrenal stimulation test was done using 50 units of ACTH in 500 cc of 5% dextrose in water over an 8 hour period. A normal response to ACTH is indicated by an increase in the 24 hour excretion of 17 hydroxycorticosteroids to 15 to 45 mg.

The patient that was receiving steroids up to the day of admission received an equivalent dose of triamcinole given in a single dose in the morning. After two weeks the total 48 hour dosage was given in a single dose in the morning on alternate days. Increments of 4 mg of the drug were made as necessary. The patients with rheumatoid arthritis and dermatomyositis were started on 8 mg of triamcinolone given in the morning in a single dose on alterate days making increments or decrements as necessary. The patients with systemic lupus erythematosus were started on 48 mg of triamcinolone in a single dose given in the morning on alternate days. Those patients with a positive P.P.D. were given 300 mg of isoniazide hydrazyde (INH) daily. During treatment all side effects were noted, and treated accordingly. On the next admission to the hospital with the purpose of repeating the endocrine studies several months after starting treatment the investigation was done as follows: The medication was discontinued upon admission. On the second hospital day a 24 hour collection of urine was

(R) Marketed as Metopirone by Ciba Pharmaceutical Co., Summit, N. J.

obtained for baseline studies followed then by the Metyrapone and ACTH tests as originally performed during the first admission.

Results

For the purpose of analysis of the data we can divide the patients into two groups. The first, Group I, included those patients receiving a low dosage of triamcinole, from 8 to 12 mg every other day in a single dose, and the second, Group II, those patients receiving a large dose of triamcinolone, 48 mg. every other day.

Group I

This group included four patients with rheumatoid arthritis (Cases 1 to 4) and one with dermatomyositis (Case 5). In all except case 3, the baseline studies for 17 ketosteroids and 17 hydroxycosteroids were normal (Table II). In case 3 these were high, as was the response to Metyrapone and ACTH stimulation. This patient is now under study for the possibility of Cushing's syndrome.

In case 1 the response to Metyrapone and ACTH was inadequate. This is attributed to the fact that she was receiving prednisone, 10 mg daily for the previous five months. In the other four patients both adrenal and pituitary reserve were adequate (Table II).

These patients received from 8 to 12 mg of triamcinolone in a single dose every other day. Adrenal and pituitary reserve were tested again in 2 to 6 months (Table III). Again case 3 shows high values. The other patients showed normal results. Case 5, a patient with dermatomyositis, underwent an operation under general anesthesia for his knee condition, tolerating the procedure well without the need to use cortisone. Case 2 suffered an acute myocar-

TABLE II: STUDIES BEFORE TREATMENT

Case No.	Baseline Study		Metopyrone Tests		ACTH Test	
	17 Keto	*17 Hydoxy*	*17 Keto*	*17 Hydoxy*	*17 Keto*	*17 Hydoxy*
1	13.30	4.54	10.30	3.80	8.40	15.56
			7.60	6.50	6.60	12.90
2	5.10	8.78	3.20	15.35	10.90	27.40
3	19.58	20.40	37.05	73.95	26.82	23.78
			34.17	56.57	23.52	35.04
4	11.41	7.98	9.25	8.32	13.60	21.45
			9.40	18.30		
5	17.30	10.30	17.10	22.90	18.68	10.50
			22.62	16.90	14.81	25.80
6	15.66	9.72	19.20	12.00	15.30	18.40
			8.83	13.90	19.78	27.30
7	11.77	10.50	9.36	9.48	7.15	15.81
			5.25	3.50	8.00	22.45
8	5.70	0.26	8.40	5.70	17.06	33.20
			5.53	7.40	15.62	24.60
9	9.99	11.12	9.50	8.35	12.21	18.35
			11.93	18.14		
10	12.98	3.40	12.52	13.28	19.98	28.56
			9.84	17.84	14.97	25.34

TABLE III: STUDIES AFTER TREATMENT

Case No.	Dose (*mg*)	Duration (*Months*)	Baseline Study		Metopyrone Test		Acth Test	
			17 Keto	*17 Hydroxy*	*17 Keto*	*17 Hydroxy*	*17 Keto*	*17 Hydroxy*
1	8-40							
2	12	5	14.90	19.50	17.90	19.90	29.70	31.30
					18.90	28.30	22.00	38.90
3	8	6	30.00	12.00	46.50	31.90	18.09	12.60
					36.75	36.90	26.20	29.40
4	12	2	11.40	6.90	14.40	14.80	19.90	28.60
					14.10	40.50	13.30	15.90
5	12	6	8.40	4.60	12.80	12.20	18.60	26.80
6	48	6	4.76	5.00	12.53	30.30	13.47	41.10
					4.42	13.60	9.49	29.60
7	48	3	7.25	9.40	6.66	25.80	6.46	15.98
					4.17	11.80	10.04	55.38
8	48	6	4.90	1.22	6.08	8.10	9.02	4.76
					18.25	8.20	11.70	24.80
9	48	4	3.65	2.00	5.60	5.07	11.08	30.00
					6.70	16.86	8.75	23.20
10	48	6	4.73	2.45	6.58	6.23	22.75	15.48
					8.02	5.85	14.98	17.36

dial infarction tolerating the initial stressful situation well without the need of additional cortisone. She died two weeks after the episode, of cardiac rupture and tamponade.

The response to therapy was good in only 3 of the 5 patients, cases 3, 4 and 5. In case 1 the symptoms and signs could not be suppressed even in the doses of 40 mg, on the other hand 4 to 8 mg daily controlled well her symptomatology. Case 2 required large doses of aspirin to supplement the 12 mg of triamcinolone every other day. Both patients had previously received steroid therapy.

Of the 4 patients tested, 3 showed a normal pituitary ACTH reserve as demonstrated by a three to six fold increase in the urinary hydroxycorticosteroids after Metyrapone administration. Patient number 2 showed a limited reserve. The adrenal reserve was excellent in all 4 as shown by the response to ACTH administration.

Group II

This group includes 5 patients with systemic lupus erythematosus. Case 10 has never shown positive L.E. cell preparations, but the diagnoses is fairly definite as he has rheumatoid-like arthritis, butterfly rash, and probably nephritis.

None of them had received previous corticosteroid therapy. In all the disease was of recent onset, the duration of symptoms varying between 2 and 3 months. They all have severe disease, some with lupus nephritis (Table IV). One of the patients, case 7, also had a severe polymyositis. They received 48 mg of triamcinolone every other day in a single dose.

All the patients responded well to the every other day dosage schedule. After one year all but one, are alive. The only death was case 6. Initially this patient showed a

TABLE IV: RENAL FUNCTION STUDIES BEFORE TREATMENT IN GROUP II

Case No.	Urinalysis	Bun (mg.%)	Creatinine Clearance (ml./min.)	Renogram	Renal Biopsy
6	Albuminuria Pyuria Hematuria	32	64	Pseudo-obstructive	Glomerulo-nephritis
7	Albuminuria Pyuria Hematuria	26	78	Pseudo-obstructive	Glomerulo-nephritis
8	Albuminuria Pyuria Hematuria	15	70	Pseudo-obstructive	Not done
9	Negative	15	66	Class III	Glomerulitis
10	Hematuria Albuminuria	12	112	Normal	Inadequate

good response. Six months later and after steroid therapy was discontinued for two weeks with the purpose of repeating the endocrine studies she developed an exacerbation of the disease with severe cerebral arteritis, coma and death despite high doses of daily steroid therapy.

All these patients showed well preserved pituitary and adrenal function after 2 to 6 months of treatment with this high dosage (Table III). Furthermore, no complications from treatment were observed. There has been no case of infection, peptic ulceration, nor pathologic fractures. Only minimal Cushingoid features developed in some, except one patient who developed marked rounding of the face and acne.

The response to Metyrapone was low in 3 patients before treatment (Cases 6, 7 and 9). The only explanation we can offer for this is the posibility of pituitary insufficiency secondary to lupus vasculitis. In all patients, the response to Metyrapone was normal after treatment (Table III), probably the result of improvement of pituitary function with treatment. The response to ACTH was excellent both before and after treatment denoting normal adrenal reserve.

It is clear from our results that both adrenal and pituitary function are well preserved despite large doses of triamcinolone administered in a single dose every 48 hours for prolonged periods of time, even though there is a tendency for the baseline excretion of 17 hydroxycorticosteroids to be lower after treatment.

Discussion

In 1952 Fraser, Preuss and Bigford (11) reported the first death of a patient that had been receiving cortisone and underwent surgery. This patient died in shock secondary to unresponsive adrenal glands to the stress of the surgical procedure. Since then many studies (12, 13, 14) have shown that when corticosteroids are administered even for short periods of time, adrenal and or pituitary suppresion occurs

which may last as long as six months to a year after the drug is discontinued. It is important in these patients to administer cortisone during periods of stress such as surgery, infection, and myocardial infarction because of possible failure of adrenal and pituitary response and death from shock. Ocasionally adrenal pituitary unresponsiveness may be permanent but this is rather rare.

It has been shown by others (4, 6) that corticosteriods administered on an every other day single dose schedule are effective in controlling clinical manifestations of disease in a large percentage of patients. This is specially so in patients who have not previously received these compounds. They are more efective in dermatologic and allergic conditions. It has also been shown that side effects are much less frequent. These same authors showed that adrenal function was preserved when prednisone is used in this manner. They re ported on several patients that tolerated well surgery under general anesthesia without requiring cortisone administration. Two of our patients tolerated well stressful situations without the need of supplementary cortisone, one a surgical procedure under general anesthesia, and the other a myocardial infarction.

As far as response to treatment this series is small and we can not arrive at any definite conclusions. We have been impressed, however, with the response to this form of therapy of patients with systemic lupus erythematosus. The five patients treated were seriously ill and some had lupus nepritis. Only one patient died as the result of a cerebral vasculitis after the triamcinolone was discontinued for 2 weeks with the purpose of repeating the endocrine studies. In all patients a remission was induced with doses of 48 mg every other day in a single dose. This dosage was continued for a minimum period of 6 months and then gradually reduced, 2 to 4 mg every two weeks to a maintenance dose of 8 to 16 mg. Except for the development of Cushingoid appearance in these patients there were no serious complications from this form of therapy. Our previous experience in patients with lupus nephritis on daily corticosteroid therapy at this high dosage level was very dissapointing. The patient's underlying disease responded to therapy; complications, however, were frequent, specially sepsis. In none of these 5 patients did superimposed infection develop. None of them developed peptic ulcer diseases or appreciable osteoporosis.

Twenty four hour urine 17 ketosteroid excretion was normal prior to steroid therapy (Table II). After therapy there was a tendency for them to be lower (Table III). The response of the 17 ketosteroid 24 hour excretion to the Metyrapone test and to ACTH stimulation was erratic and inadequate. In only one patient was the excretion over 20 mg during Metyrapone, and in only 2 after ACTH stimulation. Our findings corroborate those of others (15, 16, 17) that determination of 17 ketosteroid excretion as a measure of adrenal and pituitary function with the Metyrapone and ACTH tests is inadequate.

Twenty four hour 17 hydroxycorticosteroid excretion before treatment was normal in all except 2 patients (Table II). In all patients except case 2 the 24 hour excretion of 17 hydroxycorticosteroid was lower in the post-treatment period (Table III). These findings may indicate some degree of diminished reserve.

Summary

Ten patients with connective tisue diseases were studied, 4 with rheumatoid arthritis, 1 with dermatomyositis and 5 with systemic lupus erythematosus. Adrenal and pituitary function was determined using the ACTH and the Metyrapone tests before and 2 to 6 months after treatment with triamcinolone on an every other day single dose schedule. The patients with rheumatoid arthritis received from 8 to 12 mg and those with systemic lupus erythematosus 48 mg of the drug every other day.

One patient, case 3, showed high baseline excretion of 17 ketosteroids and 17 hydroxycorticosteroids and a marked response to ACTH stimulation and is at present under study for the possibility of Cushing's syndrome. The other patients showed normal adrenal and pituitary reserve after treatment. The results of the 17 ketosteroid excretion was erratic and unpredictable while that of 17 hydroxycorticosteroid revealed more adequate and predictable results.

Although the series is small and reliable conclusions as to results of therapy can not be drawn we were impressed by the excellent response of the patients with systemic lupus erythematosus to high doses of triamcinolone given every other day in a single dose without the development of complications from therapy, specially sepsis, as was previously our experience with daily dosage. All but one of these 5 patients are living after one year despite the presence of severe lupus nephritis at the onset of the disease in 3 of them.

One patient tolerated well a surgical procedure under general anesthesia, and another the acute phase of a myocardial infarction without the need for supplementary cortisone.

Resumen

Diez pacientes con enfermedades reumáticas fueron estudiados, 4 con artritis reumatoidea, 1 con dermatomiositis y 5 con lupus eritematosus sistémico. La función de la pituitaria y de la adrenal fue estudiada usando las pruebas de ACTH y Metopirona respectivamente antes y de 2 a 6 meses después de tratamiento con triamcinolona administrada por la via oral en una sola dosis en días alternos. A los pacientes con artritis reumatoide se le administraba de 8 a 12 mg. y a los de lupus eritematosus 48 mg.

Un paciente, el caso no. 3, demostró excreciones altas de 17 cetosteroides y 17 hidroxicorticosteroides y una respuesta exagerada a la estimulación con ACTH. Al presente este enfermo se encuentra bajo estudio para eliminar la posibilidad del síndrome de Cushings. Los otros enfermos demostraron reserva pituitárica y adrenal normal después de tratamiento. Los resultados de la excreción de los 17 cetosteroides erráticos e impredecibles en contradicción a los 17 hidroxicorticosteroides.

Aunque el número de casos estudiados es pequeño y no se puede llegar a conclusiones definitivas en cuanto a resultados con esta forma de tratamiento, nos ha impresionado el efecto satisfactorio de esta forma de tratamiento en los enfermos con lupus eritematosus sistémico sin observarse las complicaciones que anteriormente se observaban cuando se administraban estas dosis altas diariamente, y en especial sepsis. Todos menos uno de estos pacientes están vivos después de un año de tratamiento a pesar de haber tenido nefritis severa al co-

mienzo de su enfermedad.

Uno de los enfermos toleró muy bien una operación bajo anestesia general y otro la fase aguda de un infarto del miocardio sin la necesidad de administrar cortisona.

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GRAND ROUNDS, UNIVERSITY HOSPITAL

G6PD Deficiency

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Edited by Norman I. Maldonado, MD

Case Presentation

Dr. Ezequiel Rivera:*

A 25 year old Negro male was first seen at the Hematology Clinic in 1963 complaining of having intermittent episodes of yellowish sclerae associated with "Coca-Cola"-like urine. There was no history of nausea, vomiting, abdominal pain, fever, chills, anorexia, blood transfusions, drug ingestion, contact with hepatitis or history of jaundice in the past. The patient stated that is sclerae had been yellowish since 1960. The patient had bronchial asthma and received medication for this co dition periodically. He denied taking any medica ions during the recent months. There was no family history of anemia, jaundice or any other hematologic disease.

Physical examination revealed a well-developed, well-nourished man in no acute distress, alert and cooperative. The blood pressure was 100/70 mm Hg, the pulse was 76/minute and regular. Conjunctivae were icteric. The ears, nose and heart were normal. The liver was palpable just below the right costal margin and at the xyphoid, with minimal tenderness to palpitation. The spleen was not palpable. The genitalia and rectal examination were normal. The skin showed no purpura.

The laboratory work-up in 1963 revealed a hemoglobin of 14 g/100 ml.; leukocytes 11, 370 mm^3, and platelets 475,000/mm^3. The urine analysis and stools for ova and parasites were negative. Blood glucose was 65 mg % BUN 9 mg %; SGOT, 28 units; SGPT, 34 units, total bilirubin 6.2 mg % with 0.4 mg direct reacting. The prothrombin time was 14 seconds with a control of 12 and the bleeding times were normal. The serum cholesterol was 175 mg % and the total protein was 7.25g% with 4.25 albumin. The alkaline phosphatase was 18.5 KA units. A chest X-ray and the electrocardiogram were normal.

In 1964 a sickle cell preparation was negative. The Coomb's test was negative. The hemoglobin electrophoresis revealed hemoglobin A. A repeat hemoglobin was 13.2 gms/100 ml and the reticulocyte count was 7.8%. A ^{51}Cr RBC survival showed a T-½ of 15 days.

In 1967 his hemoglobin was 14.3 g/100 ml, the WBC was 11,900 with a normal differential. The peripheral smear revealed slight anisocytosis, stippled cells, abundant platelets, and several hypersegmented polymorphonuclear leukocytes. The reticulocyte count was 11.8%. A Heinz body preparation after incubation with phenylhydrazine revealed gross deficiency. A glutathione level was 42 mg/100 ml. and after incubation with acetyl phenylhydrazine the level dropped to 7 mg per 100 ml. An autohemolysis test revealed marked hemolysis with complete correction after the addition of glucose. A sugar-water test was negative and a liver biopsy revealed slight bile stasis

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This presentation was supported by Hematology Training Grant No. T1 AM 5302-05.

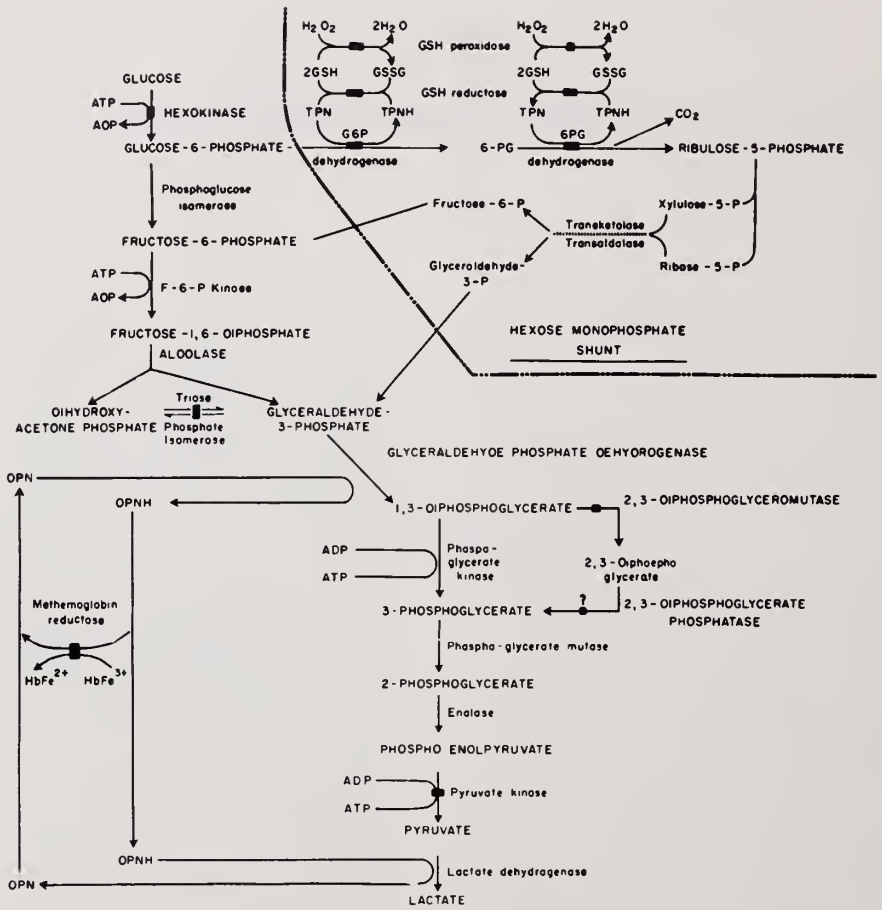
in the central areas. The patient's condition has remained unchanged since he was first seen in our clinic. He continues to be jaundiced but his hemoglobin has been stable. At the present he is on no therapy.

Discussion

This patient is of some interest in that he is representative of the red cell enzyme defect first described by Alving, Beutler, and associates (1) Doctor Alving was initially interested in the treatment of malaria. It had been observed in Korea that about 10% of all Negro servicemen exposed to the antimalarial agent, primaquine, developed a marked and rather severe hemolytic episode. (2) In an attempt to demonstrate the mechanism of this hemolysis, Alving and co-workers delineated the enzymatic defect which we now term glucose-6-phosphate dehydrogenase (G6PD) deficiency. Before discussing this specific enzyme defect, I would like to review very briefly the biochemistry of the red cell.

The metabolism of glucose in the mature human erythrocyte is outlined in Figure I. The mature erythrocyte has neither nucleus nor mitochondria, and all of its energy requirements are derived from the anaerobic oxidation of glucose. Glucose is phosphorylated and then is metabolized to lactate. Metabolism via the pathway from glucose through fructose-6-phosphate to lactate constitutes about 90% of the metabolism of glucose in the red cell. In this pathway adenosine tri-phosphate (ATP) is produced at two steps and there is a net production of two moles of lactate and two moles of ATP per mole of glucose utilized. The ATP produced is necessary for the maintenance of the normal configuration and ionic concentrations of the red cell. Any defect in this pathway will result in a deficiency in the energy metabolism of the red cell. There is an alternative pathway, the so-called hexose monophosphate shunt. Glucose-6-phosphate is reduced and decarboxylated to ribulose-5-phosphate. The 5-carbon sugars resulting from isomerization are then metabolized primarily to glyceraldehyde-3-phosphate, where they re-enter the glycolytic pathway. Normally, less than 10% of the glucose is metabolized by way of the hexose monophosphate shunt. Although it serves only a limited function in terms of overall glucose metabolism, the shunt is extremely important in that it is the only pathway in which reduced triphosphopyridine nucleotide is produced. This co-factor appears to play an important role in the detoxification of exidizing componds within the red cell. The concentration of oxygen within the mature red cell, of course, is very high. Oxygen in the presence of hemoglobin and ascorbic acid produces peroxides. In the diagram I have outlined hydrogen peroxide, but other peroxides can oxidize the various bonds of proteins within the red cell, resulting in their precipitation and denaturation. It is the function, or at least one of the functions, of reduced triphosphopyridine nucleotide (TPNH) to protect the red cell against such oxidation. Peroxides are normally present within all cells. In addition, sensitive cells can be damaged by agents such as sulfonamides, primaquine and other drugs, which also have oxidative capabilities. It is usually thought, and there is pretty good evidence, that TPNH generated by the hexose monophosphate pathway also protects the red cell against the oxidative effect of these agents.

There is a third metabolic activity which is very important within the red cell; the



METABOLISM OF GLUCOSE IN THE ERYTHROCYTE

Fig. 1: **Carbohydrate metabolism in the mature human erythrocyte.**

reduction of methemoglobin. Hemoglobin in the functional state is present in the ferrous form. However, in the presence of oxidizing agents such as 0_2, hemoglobin iron is slowly oxidized to the ferric form (methemoglobin). The lattter is incapable of the reversable association with molecular oxygen. Reduction of methemoglobin is carried out primarily by the DPNH-dependent enzyme methemoglobin reductase. The generation of DPNH from DPN is linked to glyceraldehyde phosphate dehydrogenase. A deficiency of the enzyme methemoglobin reductase results in a constant methemoglobinemia within the red cell. Patients heterozygous for this enzyme deficiency are cyanotic. The cyanosis is due to an enzyme deficiency rather than to an intrinsic defect in the hemoglobin molecule itelf. Methemoglobin reductase deficiency is an extremely rare cause of cyanosis and we won't discuss it any further.

I would like to return to the problem presented by the patient under discussion today. It is apparent from the case presentation that he had some form of erythrocyte glucose-6-phosphate deficiency (G6PD deficiency).

In the patients originally described by Alving, Beutler, and coworkers, (1) the drug-induced hemolytic episode could be divided into three phases. Initially the hemoglobin and reticulocyte count was within normal limits. Red cell survival, using the chromium (51) technique revealed a T½ of about 25 days, indicating little or no hemolysis under basal conditions. The subject was then exposed to a drug such as primaquine. Within three days the patient developed signs and symptoms of hemolysis. His hemoglobin rapidly dropped to about two-thirds of the initial level, the reticulocyte count rose and the red cell survival became markedly shortened. If drug administration was continued in this original group of subjects, they entered the recovery phase. The hemoglobin slowly rose, the reticulocyte count, after reaching a level of 7.5 to 10½, slowly fell, and the red cell survival began to approach normal values. Finally, the drug-treated patients reached what is called the equilibrium phase. The only signs of hemolysis were a slightly increased reticulocyte count and a mild, but definite, shortening of the red cell survival.

Further studies indicated that the hemolytic episode was due to an intrinsic defect of the red cell. The first definite abnormality which was found to be associated with the hemolytic state was the presence of Heinz bodies (Fig. 2). It was found by Beutler et al. that episodes of hemolysis were associated with the presence in the peripheral blood of numerous red cells containing these intra-cellular precipitates. (3) The presence of Heinz bodies provided these workers with their first clue— the presence of precipitated hemoglobin suggested the presence of either an unstable hemoglobin molecule or a deficiency in the mechanisms which normally protect the hemoglobin molecule from denaturation. They knew that there was nothing wrong with the hemoglobin molecule itself so they reasoned that the biochemical defect must result, under some conditions, in the precipitation of normal hemoglobin. It was next discovered that this phenomenon could be reproduced in the red cells of sensitive individuals if these cells were incubated *in vitro* with an oxidizing agent such as acetylphenylhydrazine. Beutler and his coworkers found that if one incubated red cells from sensitive individuals (individuals who had undergone drug-induced hemolysis and who had recovered) with acetylphenylhydrazine (AP H) for several hours, numerous Heinz bodies appeared within a majority of the red cells whereas in erythrocytes from normal individuals only a few Heinz bodies appeared on incubation with acetylphenylhydrazine. Beutler et al. (4, 5) then mea-

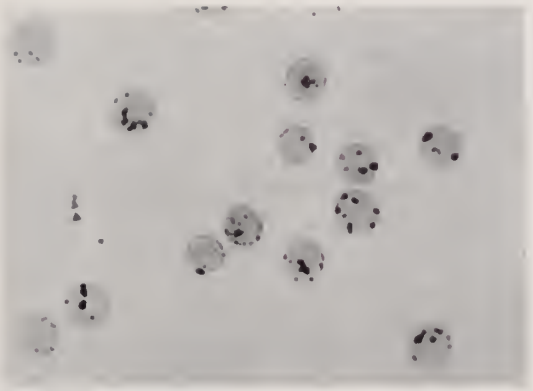


Fig. 2: Heinz bodies.

sured the concentration of various oxidizable compounds within the red cell during Heinz body induced hemolytic anemia. They found that the concentration of one of these chemicals, reduced glutathione (GSH) dropped markedly in concentration during incubation with APH. Normally, the red cell contains between 50-80 mg per 100 ml. of reduced glutathione. If normal red cells are incubated with acetylphenylhydrazine for several hours the concentration of GSH remains essentially unchanged, in contrast to red cells from sensitive individuals where the concentration rapidly falls under these *in vitro* conditions. In fact, red cells from the patient who was presented this morning had an initial concentration of 42 mg.% and a concentration after 2 hours of 7 mg.% — a marked drop in the concentration of reduced glutathione. So, what has happened? The red cells contain a metabolic pathway by which the concentration of reduced glutathione is maintained through the action of the co-factor TPNH. When TPNH is deficient for any reason, the concentration of reduced glutathione rapidly drops in the presence of oxidizing agents.

We now have an idea of what happens in the presence of the drug (Fig. 3). In the normal cell glucose 6- phosphate, in the presence of the enzyme glucose-6-phosphate dehydrogenase, is converted to 6-phosphogluconate; triphosphopyridine nucleotide (TPN) is reduced to TPNH. TPNH in the presence of glutathione reacts with an oxidizing agent and detoxifies it (probably via several additional steps — see below). In the cell in which this pathway does not operate or is deficient, the drug or oxidizing agent, signified by the quinone ring, reacts directly

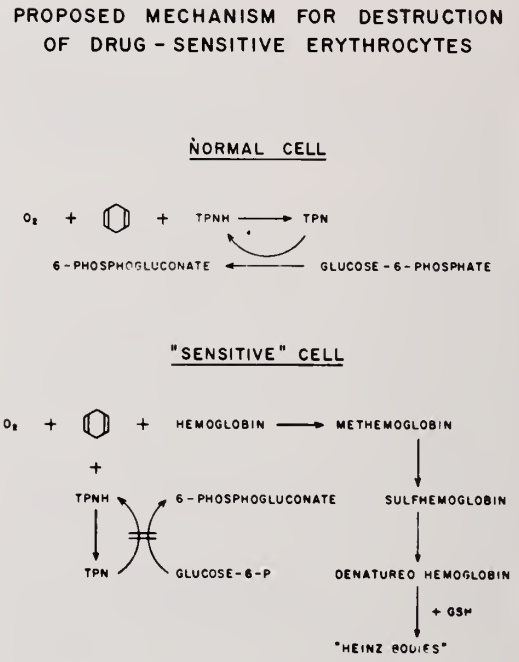


Fig. 3: Postulated mechanism of drug-induced red cell damage.

with hemoglobin instead of with the GSH and TPNH, forming methemoglobin, sulfhemoglobin, and finally precipitated hemoglobin or Heinz bodies. In essence, therefore, this system acts as kind of a first line of defense against the oxidizing effects of drugs as well as hydrogen peroxide. There are a number of drugs which can do this. Some of these are listed in (Fig. 4.) They include the 8-aminoquinolines, and primaquine is probably the most widely used. In addition to these, we have the sulfonamides, i. e. Gantrisin, ® Azulfidine®, Kynex®, all drugs which are commonly used in medical practice. Acetanilid, acetylphenylhydrazine, and phenacetin are also very common agents. Benemid,® para-aminosalycilic acid and aspirin itself may all cause hemolysis when given in high enough do-

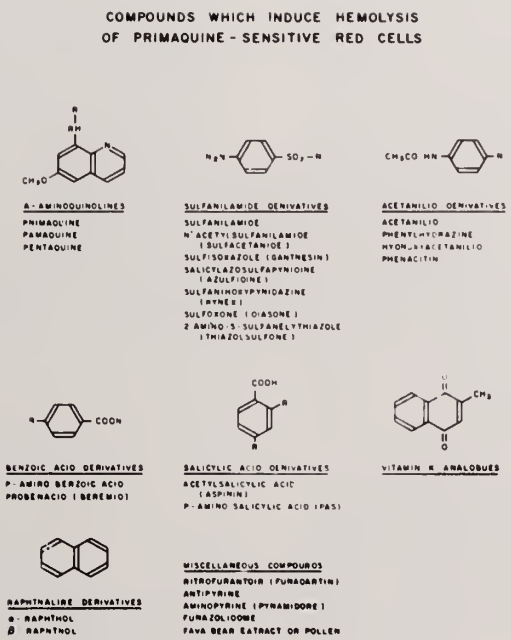


Fig. 4: Drugs capable of inducing hemolysis in susceptible individuals.

sages. Vitamin K analogues and naphthalene derivatives are notorious in inducing hemolysis in sensitive infants. All of these agents and more have been known to induce acute hemolytic episodes in sensitive individuals. As you can see this is a problem which one can encounter in everyday clinical practice. I am often asked whether there is any way by which I can predict whether a new drug which has been introduced is going to induce hemolysis in sensitive individuals. Although I can't predict with certainty, I suspect that any agent which has a semi-quinone ring with an oxidizable or ionizable side group can potentially act as a hemolytic agent.

The original studies done in American Negroes suggested that primaquine sensitivity or G6PD deficiency was a sex linked defect. (6) In other words, the gene for the abnormal enzyme is carried on the X chromosome. Males will be severely affected. Females can be either heterozygous or homozygous. The heterozygous state,

one normal gene and one abnormal gene, would be much more common, but because of the peculiarities of the inheritance and expression of the X gene in the female, the enzyme defect in the heterozygote females varies in severity all the way from practically completely deficient to almost normal. It is very difficult to predict, even knowing the genetic make-up of a female, what her red cell G6PD level will be.

The defect was initially found in American Negroes; (7, 8) however, since then it has been found in many other population groups. (9) In Fig. 5 you can see that GSH instability, or G6PD deficiency, has been observed in Africa, Italy, Sardinia, the Middle East, India, Southeast Asia, and even in New Guinea and the northern parts of Australia. So, this is a rather widespread disease. In general, it follows roughly the distribution of endemic malaria. Areas in which malaria has been hyperendemic in the past tend to have a relatively high concentration of individuals with G6PD deficiency. The exact relationship between G6PD deficiency and malaria has not been well worked out, but it has been suggested that a reduced rate of metabolism through the hexose-monophosphate shunt, secondary to the deficiency of the enzyme G6PD, has provided an environment which the malarial parasite finds unfavorable. Therefore, this defect has provided a protective effect against the ravages

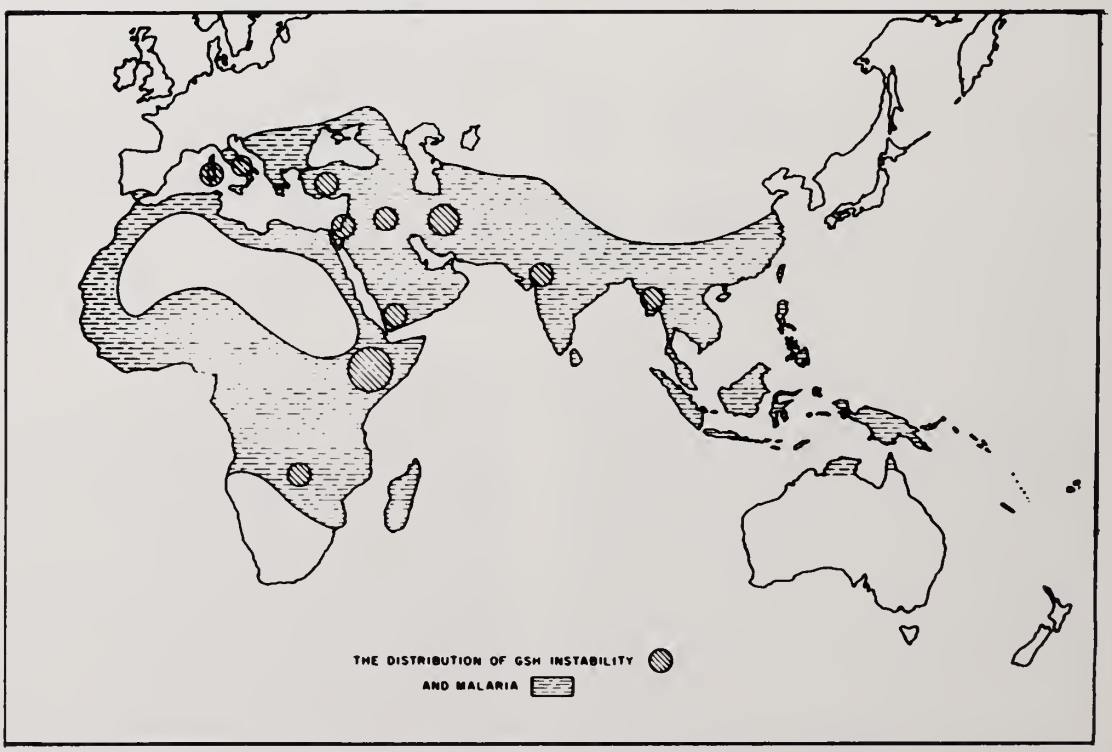


Fig. 5: Geographic distribution of erythrocyte G6PD deficiency (GSH instability) and malaria in the Old World.

of malaria. Although the evidence is suggestive, the hypothesis remains to be proved.

I have described the "Negro" type of the disease associated with self-limited hemolytic episodes. The disease is really not very severe unless the patient initially is very anemic. In other words, if one starts with an individual with a normal hemoglobin concentration and hemolyzes one-third of his red cell mass, the clinical effects are usually not disastrous. But if a patient initially has a hemoglobin of 8 g/100 ml and hemolyzes 1/3 of his red cell mass, he may find himself in considerable trouble. Even so, hemolysis is self limited in these individuals because, in this variant of the defect, only the older red cells have a low content of the enzyme; the young red cells, including the reticulocytes, have an almost normal concentration of the enzyme. Because of this, as soon as the older cells are hemolyzed, a new equilibrium is attained associated with a slightly shortened red cell survival and a mild increase in the percentage of reticulocytes. There are other variants known and, although less common, they are important. A general classification is shown in Fig. 6.

In the "Negro" type, there is moderate reduction in the enzyme level in the red cell. The level of the enzyme in the white cell is almost normal. In the absence of drug ingestion hemolysis is minimal and almost impossible to detect. There is another type of G6PD deficiency found in Caucasians usually from the Mediterranean area in whom there is a moderate to marked reduction in the red cell enzyme levels, associated with (some what) decreased white cell G6PD activity. These individuals have a well-defined, compensated hemolytic process. Because of the marked reduction in the red cell enzyme levels, a reduction which extends even into the young cell population, these patients when exposed to a hemolyzing agent will continue to hemolyze as long as the exposure to the offending drug continues. I have seen a patient drop to less than 4 of hemoglobin because of continued exposure to a sulfa derivative. So one cannot say *per se* that the hemolysis associated with G6PD deficiency is a self limited process. Finally, there is a, "Caucasian" type, found mainly in Northern European, in which there is practically no red cell enzyme activity detectable, and in which the white cell activity is again reduced. These patients are anemic and exhibit a constant hemolytic process even in the absence of any known hemolyzing agent. It is probable that the endogenous production of oxidizing agents produced within these red cells is sufficient to induce Heinz body formation and constant destruction of older cells. Clinically these patients have a form of congenital nonspherocytic hemolytic anemia. The patient whom we are discussing today does not really fit the usual "Negro" type of deficiency, because even in the absence of obvious hemolyzing agents he still has a compensated hemolytic process. In addition, the levels of G6PD activity within his red cells appear to lie well below the usual

TYPES OF G6PD DEFICIENCY IN MALES

	GROUP	ENZYME LEVEL: RED CELL	ENZYME LEVEL: WBC	HEMOLYTIC PROCESS
1.	AMERICAN NEGRO	MDDERATE REDUCTIDN	NDRMAL	CDMPENSATED
2.	CAUCASIAN	MDDERATE TD MARKED REDUCTIDN	REDUCED	COMPENSATED
3.	CAUCASIAN	MARKED REDUCTIDN TD ABSENT ACTIVITY	REDUCED	MAY BE ANEMIC

Fig. 6: A general classification of the various clinical types of G6PD deficiency.

range for this group. I would judge that he fits better into the "Mediterranean" classification and would predict that he would be quite sensitive to the hemolytic action of the agents listed in Fig. 4.

These three categories cover the clinical variants associated with this enzyme deficiency. Further classification can be made on the basis of the biochemical characteristics of the numerous G6PD enzyme variants which have been identified. Such characteristics include electrophoretic mobility, affinity of the enzyme for glucose-6-phosphate, deoxyglucose-6-phosphate and T PN, and pH optima. The enzyme mutants which have been identified (about 20 thus far) vary widely in essential characteristics such as rate of enzyme synthesis, stability *in vivo,* and efficiency in activity. The interaction of these various characteristics re reflected in each case in the clinical syn- rome. Thus, a mutation which results in a ered electrophoretic mobility without ar change in the enzyme kinetics is as- ated with no clinical symptomatology. On the other hand, a mutation which affects either the rate of synthesis of a structurally normal enzyme or which leads to the synthesis of a form which is unduly susceptible to *in vivo* inactivation will lead to various degrees of clinical symptomatology. Unfortunately little is known of the protein structure of this enzyme so we are unable to relate changes in function to amino acid substitutions in the peptide chains (such as is possible for hemoglobin variants).

Several other inherited defects have also been found in the hexose monophosphate shunt of the erythrocyte. One of these, glutathione peroxidase deficiency, has recently been observed in association with hyperbilirubinemia of the newborn. The clinical course of a typical infant with this syndrome is shown in Fig. 7. This was a baby who was transferred to our hospital because of hyperbilirubinemia; at the time of admission the serum bilirubin was about

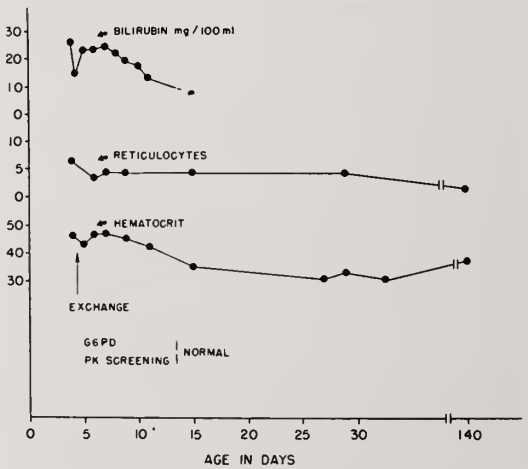


Fig. 7: The clinical course of a newborn infant with partial GSH-peroxidase deficiency.

26 mg %. In addition, there was some evidence of a hemolytic process: his reticulocyte count was about 6%, and his hematocrit was 47%. Erythrocyte G6PD and pyruvic kinase screening tests were normal. There was no evidence of feto-maternal immunological incompatibility. The baby did not appear to be septic, but because of the hyperbilirubinemia he underwent an exchange transfusion. His bilirubin stabilized and rapidly fell and when the patient was again seen at age 140 days, his hematocrit was normal, the reticulocyte count had fallen to about 1½% and the baby appeared in all respects healthy. Investigation of his red cells at the time of the exchange transfusion revealed that this baby had a partial deficiency of the enzyme glutathione peroxidase. The enzyme pathway involved is shown in Fig. 8. This is a schematic draw-

ing of the cycle of detoxification of peroxides. Again here, for simplicity sake, I have shown hydrogen peroxide but remember that this can be any peroxide or an oxidizing drug. The mechanism of red cell damage by each of these agents is thought to be similar. Glucose-6-phosphate is metabolized in the presence of G6PD to 6-phosphogluconate and reduces TPN to TPNH. This TPNH then, in the presence of glutathione reductase, reduces oxidized glutathione to reduced glutathione. The latter, in the presence of glutathione peroxidase, interacts with peroxide to form water and again oxidized glutathione. Any defect in any one of these 3 enzymes will lead to a similar clinical picture, i.e. drug-induced hemolytic anemia, the formation of Heinz bodies, and glutathione instability on *in vitro* incubation with acetylphenylhydrazine.

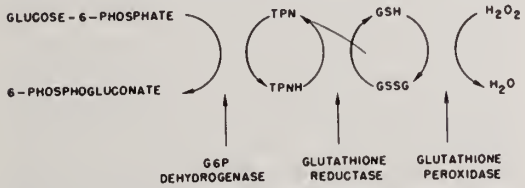


Fig. 8: The metabolic pathway of peroxide detoxification in the human erythrocyte.

Red cell glutathione peroxidase appears to be somewhat reduced in the normal newborn. The enzyme levels in various clinical states are shown in Fig. 9. The enzyme activity is much less in cord blood of normal full-term newborns than that found in normal adults. As these infants grow older (0 - 6 months of age) the activity increases to a level somewhat intermediate between the adult and the cord blood level. The change of red cell GSH-peroxidase activity with age is illustrated in Fig. 10. The starred points represent 3 infants who had

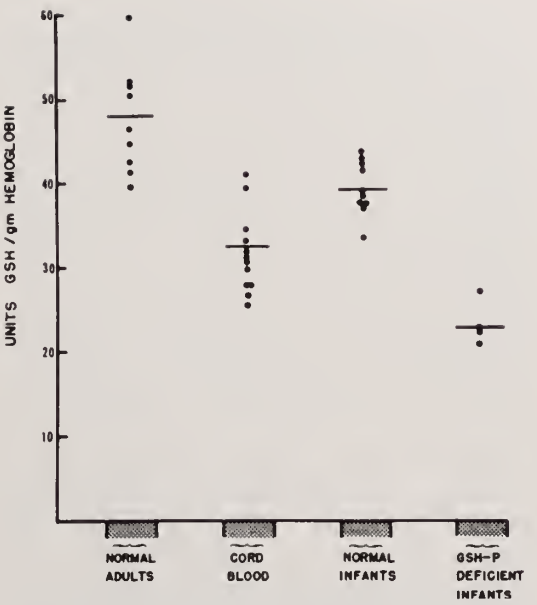


Fig. 9: Red cell levels of glutathione peroxidase activity in the normal adult, newborn infant, and partially deficient infant.

non-immunologic hyperbilirubinemia in the newborn period associated with an increased susceptibility to Heinz body formation. It is evident that even after several months, the enzyme activity remains distnctly low. These children are considered to be heterozygous for this genetically determined deficiency.

It appears that there exists in erythrocytes a critical level of GSH peroxidase activity below which spontaneous Heinz body formation and hemolysis occurs. This is especially true in the newborn period when an alternative pathway for the detoxification of hydrogen peroxide, the catalase system, also has not reached maximal activity. The red cells from normal newborn infants thus are especially susceptible to the action of oxidizing agents. However, the enzyme levels in the normals appear to be sufficient

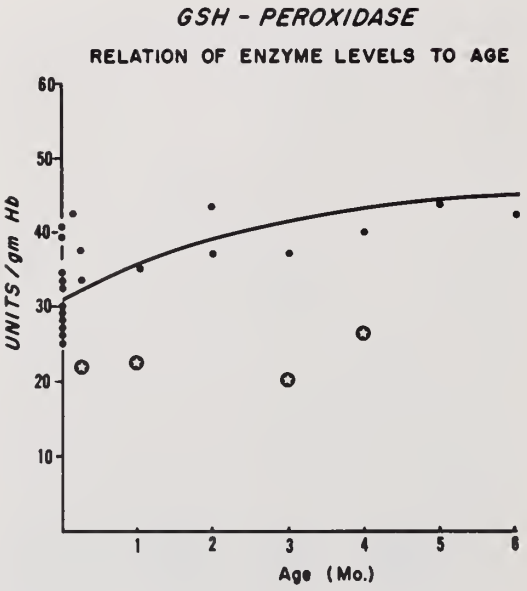


Fig. 10: The change in erythrocyte GSH-peroxidase activity during the first 6 months of life.

to protect the red cell from the effects of endogenously produced peroxides. In the presence of even a moderate rduction of enzyme activity, associated with an inherited defect of the enzyme, spontaneous Heinz body formation and hemolysis becomes clinically important. As these deficient infants become older, the red cell enzyme level slowly rises and they enter the range where the red cells are less susceptible to th effects of endogenous peroxides. Clinical hemolysis ceases. If, however, these infants are exposed to large doses of exogenous oxidizing agents such as sulfonamide, they appear to develop a mild hemolytic process, similar to that seen with G6PD deficient individuals.

We have recently also seen a patient whom we believe to be homozygous for glutathione peroxidase deficiency. This patient, indeed, was originally seen in this hosmal shape and form of the red cell. The pital. He was brought to Dr. Norman Maldonado's attention because he had developed a hemolytic reaction following transfusion of several units of his own blood. This hemolytic episode was associated with numerous Heinz bodies in the presence of normal G6PD activity. Further studies revealed a normal level of glutathione reductase activity but glutathione peroxidase was found to be markedly decreased. Family studies revealed two siblings and both parents whose red cell GSH-peroxidase activity were in the heterozygous range. This deficiency, therefore, appears to be inherited as an autosomal recessive characteristic. The homozygous individuals appeared to be especially susceptible to hemolytic episodes.

Finally, a few cases have been described who have erythrocyte glutathione reductase deficiency. Again, the clinical symptomatology is almost identical. Most of the reported patients with glutathione reductase deficiency have been heterozygous. These patients have not hemolyzed in the absence of extraneous oxidizing agents, such as drugs. Thus, there are 3 defects, G6PD, glutathione reductase, and GSH peroxidase deficiency, the clinical symptomatology of which is rather similar, and all associated with drug sensitivity. All of these patients form Heinz bodies when their red cells are incubated *in vitro* with acetylphenylhydrazine. These three enzyme defects, plus a syndrome associated with a deficiency of glutathione, all constitute defects of the hexose monophosphate shunt.

Now I would like to turn to the consideration of the glycolytic pathway, the major pathway for energy production in the red cell. This energy is necessary for the maintenance of the normal ionic gradients and for the maintenance of the nor-

most famous and best described of these enzyme defects in the glycolytic pathway is a deficiency of the enzyme pyruvic kinase . (PK) This enzyme normally catalyzes the conversion of phospho-enol-pyruvate to pyruvic acid with the net production of one mole of ATP. Several years ago, Tanaka and Valentine described a defect of this enzyme. (10) The patients whom they originally reported had a moderately severe hemolytic anemia, frequently characterized by macrocytosis, but few other morphological abnormalities. There was splenomegaly, icterus and a hemolytic process which was not associated with any environmental agents as far as it could be determined.

Since then about 100 cases have been described, and it has become apparent that there is a wide spectrum of disease associated with erythrocyte pyruvate kinase deficiency. We have recently described two patients with this enzymopathy. The first patient had a rather severe defect. At birth he was quite jaundiced and required an exchange transfusion. When seen by us at two months of age he had evidence of a hemolytic process, but at that time his hemoglobin was 12 g./100 ml. We saw him again two months later at which time his hemoglobin was 5.0 g/100 ml, reticulocytes were about 6%, and he required a transfusion. Over the next twelve months, he required 11 more transfusions totaling over a liter of blood. At age 14 months, he underwent splenectomy; the spleen was about 5 times the normal size. Histological examination revealed marked sequestration and erythrophagocytosis, but no Heinz bodies or other inclusions could be seen within the red cell. Following splenectomy his hemoglobin, although not normal, has been maintained without transfusion in a range of about 8-9 g/100 ml, and clinically he has been well over the succeeding 2 years. His reticulocyte count has climbed markedly and in out of all proportion to his hemoglobin level, suggesting that young cells are being preferentially destroyed. This is a severe form of PK deficiency. Several patients in whom the diagnosis has not been recognized have died from their hemolytic process. This patient at the time of splenectomy had marked cardiomegaly, and it was difficult to transfuse him because of incipient cardiac failure. On the other hand, the clinical syndrome associated with this deficiency may be very mild as evidenced by the second patient. This patient came to us at the age of 28. He was originally diagnosed as having non-spherocytic hemolytic anemia in 1955. His hemoglobin was always relatively normal. In 1960 he developed acute cholecystitis and cholelithiasis, associated with a marked drop in his hemoglobin which, when he entered the hospital, was 8 g/100 ml. Following cholecystectomy, his hemoglobin returned to normal levels and remained so over the next several years. When we first saw him however, his hemoglobin concentration had slowly begun to fall. He was asymptomatic but had been turned down from a job because of anemia. The reticulocyte count was somewhat elevated and he had evidence of an uncompensated hemolytic process. He was icteric and had a spleen palpable several centimeters below the left costal margin. After initial diagnostic studies we advised splenectomy, following which, his hemoglobin had again stabilized at 15 g/100 ml. His reticulocyte count remained at about 20%, and thus has a compensated hemolytic process. He continues slightly icteric but asymptomatic. The only real problem

this patient had was acute cholecystitis. Indeed, we have identified this enzyme defect in several patients whom the surgeons asked us to see because of "premature" cholelithiasis. These patients have been entirely asymptomatic, have had a normal hemoglobin and a slightly elevated reticulocyte count, but had gall stones at an early age. So the disease may be an extremely severe one, or, on the other hand, it may be extremely mild. The enzyme levels in the red cells of all of these patients are approximately identical; one cannot differentiate them in terms of severity of disease on this basis. What we suspect is that this again represents a spectrum of mutations of an enzyme; that these are all different variants of an abnormal enzyme just as there are all different types of G6PD deficiency. Although the enzyme levels as we measure them in our artificial *in vitro* system appear uniformly low in all of these cases, some of these may have a relatively efficient enzyme *in vivo* whereas others may have a relatively inefficient one. Pyruvic kinase deficiency was initially thought to be rare. Over the last 3 years we have seen over 18 cases and don't think it is quite as uncommon as it was once considered to be.

However, there are several other defects of the glycolytic pathway which have also been described which are apparently quite uncommon. The first of these is hexokinase deficiency. Hexokinase is the first step in the metabolism of glucose. Without this enzyme, glucose cannot be phosphorylated and cannot enter into the glycolytic pathway. Hexokinase deficiency has been found to be associated with a relatively marked hemolytic anemia. As in pyruvic kinase deficiency, hexokinase deficiency is characterized by splenomegaly, and the rate of hemolysis is unrelated to drug ingestion. Interestingly enough, in the one patient we have seen the hemolytic process appeared to improve as the child grew older. We do not know whether this is a general course or whether this happens to be a peculiarity of this patient.

Finally, there is a hemolytic anemia associated with triosephosphate isomerase deficiency which I only include for the sake of completeness. The enzyme triose phosphate isomerase, is present at the junction between the glycolytic pathway and the hexose monophosphate pathway. The deficiency of this enzyme is associated with neurological symptoms and has been seen only rarely in very young children who die within the first two years of life.

It is possible to summarize these various red cell enzyme defects on the basis of the metabolic abnormalities. Dacie several years ago described the autohemolysis test and used this to classify the congenital nonspherocytic hemolytic anemias. The autohemolysis test has become somewhat archaic; but it still is useful in classifying the congenital hemolytic anemias. Essentially, this test consists of incubating red cells for 48 hours in the presence of no additives, added glucose, and added ATP. Normal cells do not hemolyze appreciably even without added glucose: hemolysis is less than 1% of the total red cells present. In Type I autohemolysis, hemolysis is increased in the absence of glucose but is corrected to normal or almost normal levels by the addition of glucose. In general, the enzyme defects characterized by defects in the hexose monophosphate pathway exhibit this type of autohemolysis. Splenomegaly is usually minimal or absent and drug-induced hemolysis with Heinz body

formation is common. The inheritance of these enzyme defects varies from sex-linked recessive for G6PD deficiency to autosomal recessive for the other defects in this group. Type II autohemolysis is characterized by increased hemolysis in the absence of glucose and a lack of correction by added glucose. Autohemolysis is corrected, at least partially, by the addition of ATP. Red cells with enzyme defects fitting into this category frequently show a decreased rate of glycolysis, a defect in the maintenance of normal concentrations of ATP, and defective energy metabolism characterized by abnormal rates of sodium and potassium ion flux across the membrane. This type is characterized by defects primarily in the glycolytic pathway. Splenomegaly is usually marked and the hemolytic process is unaffected by drugs. The mode of inheritance of this type of enzyme defect has been autosomal recessive. The carrier state in general has been associated with neither clinical nor hematological symptomatology, although it can be identified by biochemical methods.

The autohemolysis test is of interest primarily as an aid in classifying the various syndromes associated with the enzyme defects. As a diagnostic tool it has been largely supplanted by specific enzyme assays. Many of these assays require fairly elaborate and expensive biochemical techniques. However, because of their relative frequency and importance in clinical medicine, screening tests have been devised for both G6PD deficiency and PK deficiency. These screening tests require less time, are less expensive, and in general are easier to do than the definiteve enzyme assay. They are, however, limited in their diagnostic accuracy and an enzyme assay is still the *sine qua non* for a definitive diagnosis. Even the latter is subject to various errors. The most important of these potential errors results from the increased enzyme content of reticulocytes. Thus, a G6PD deficient patient who has just undergone a drug-induced hemolytic episode may have normal, or almost normal, red cell G6PD levels and the diagnosis may be missed unless he is rechecked at a later date. A similar situation may arise in PK deficiency where a markedly elevated reticulocyte count may be associated with increased enzyme activity and lead to the erroneous diagnosis of an heterozygote carrier. The latter error can be avoided if it is remembered that no well-documented case of clinical symptomatology has been reported in association with the heterozygous PK deficiency carrier.

Therapy of the congenital non-spherocyte hemolytic anemia can be divided roughly into three categories: care of the newborn, acute hemolytic episodes, and alleviation of chronic hemolysis. Congenital non-spherocytic hemolytic anemia frequently are first noted as non immunologic jaundice of the newborn. Frequently the reticulocytosis and degree of anemia may not be very marked making the diagnosis somewhat difficult. The immediate therapy is exchange transfusion dictated by the degree of hyperbilirubinemia. I tend to be somewhat conservative and usually exchange such infants when the indirect bilirubin level reaches 20 mg/100 ml. The importance in establishing an etiological diagnosis at this time lies not in the immediate decision for or against exchange; rather it lies in the long term prognosis and management. The infant with congenital non-spherocytic hemolytic anemia should be seen fairly frequently since anemia may

well be a recurrent problem. Acute hemolytic episodes are characteristically associated with drug ingestion in G6PD deficient individuals. Of greater significance is the clinical association between bacterial and viral infection with hemolytic episodes in this population. This association should be recognized since many of the drugs which are commonly used to treat such infections may in themselves lead to increased hemolysis. Viral infections may also be associated with a relative hypoplasia of the erythroid precursors. In the normal individual, such hypoplasia will lead at most to a mild transitory drop in the hematocrit of no clinical significance. On the other hand, in an individual with markedly shortened red cell survival, such hypoplasia may be associated with a dramatic fall in the hematocrit. The long-term management of individuals with red cell enzyme defects is somewhat empirical. In general, individuals with defects in the hexose monophosphate shunt do not have splenomegaly and are not benefited by splenectomy. However, an occasional exception has been reported with a good clinical response to splenectomy in individuals with CNSHA secondary to G6PD deficiency. The effect of splenectomy in individuals with defects in the red cell glycolytic pathway is controversial. Most authors have suggested that splenectomy is of little benefit in such individuals. However, our own experience is that although splenectomy is not curative, it has an important efect in alleviating the hemolytic process in individuals with PK deficiency. The transfusion requirement may be remarkably reduced or even eliminated which in itself is a significant clinical benefit. We therefore suggest this operation in any individual with CNSHA due to a defect in the glycolytic pathway and splenomegaly, especially after the patient reaches the age of 1 to 2 years.

Acknowledgement

We are grateful to Dr. Pedro Juan Santiago and Dr. Enrique Vélez-García who helped us edit this Grand Rounds. We want to thank Dr. Mercedes Torregrosa who performed the glutathione determinations.

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CARTA

CHLOROQUIN AND THE EYE

Drugs that have relatively recently been added to our medical armamentarium and which therefore have not had a chance to be exposed to the so-called test of time may sometimes affect in a more or less irreversible fashion the structural anatomy and as a result the function of certain organs or tissues of the body. One such drug is the antimalarial drug chloroquin.

Chloroquin came into the medical picture during the Second World War. It was used during the war years for the treatment of malaria. However, in the recent past it has been found to be useful in the treatment of such diseases as rheumatoid arthritis, asthma, and lupus erythematosus.

Chloroquin is a synthetic compound chemically related to the cinchona alkaloids. Its exact mode of action is not exactly known, but it has been found to accumulate readily in the tissues. In the eye, the drug is deposited in the iris, the choroid and the pigment epithelium of the retina. Acidification of the body with ammonium chloride accelerates its excretion from the tissues, so that this drug is indicated in patients presenting retinal complications produced by chloroquin.

Treatment of chronic diseases like rheumatoid arthritis requires dosages of 250 mg to 500 mg daily over periods of months or even years.

The ocular complications of chloroquin were first observed by Cambiaggi in 1957. In 1962, Henkind, who is an ophthalmologist, reported in a meeting of the American Rheumatism Association that about 15% of patients receiving the drug or derivatives showed retinopathy. Now at the most recent meeting of this society Henkind reported what is definitely a grim picture in so far as the eye is concerned: 50% of all cases show retinal damage especially if treatment is continued over a long period of time.

The changes that have been observed and that I have had the opportunity to see in a series of four cases being treated with the drug for rheumatoid arthritis by local colleagues are as follows: the retinal arterioles become constricted throughout their entire distribution and early he macula presents a sort of mottling which may progress to a point where the lesion will resemble a bull's eye. As the changes advance, the macula may in time show a generalized type of pigmentary degeneration.

There appears to be a definite correlation between the length of therapy and the incidence of the retinal lesions: the longer the period of therapy, the greater the likelihood of developing retinal lesions.

Subjectively, the patient who is developing chloroquin retinopathy, will complain of blurred vision at times, halos or a difficulty in focusing. One of my patients complained of noticing blind areas which would change in position in the visual field. Visual field changes are rare. In a few cases where visual acuity was affected because of the retinopathy drug withdrawal has not

been effective in stopping visual loss.

A keratopathy in which haziness of the corneal epithelial areas occurs in the form of punctate granular dots has occurred in a variable number of patients. This kerotopathy, however, is reversible and, therefore, need not be considered an alarming manifestation by the internist or ophthalmologist. This manifestation may, however, produce blurred vision depending on the situation of the lesions on the cornea.

In view of all of this, it should be quite apparent to the internist using this drug that precautions and a cautious use of the drug are in order. To play it safe, it would seem to me that a liaison should be established between the internist using the drug and the ophthalmologist of his confidence so that possible irreversible damage of the nature described may be avoided.

Roberto Buxeda, MD

EDITORIALES

LOS ANTIPALUDICOS EN LAS ENFERMEDADES REUMATICAS

En este mismo número aparece una carta del Dr. Roberto Buxeda donde informa sobre el desarrollo de una retinopatía secundaria al uso de cloroquina en 4 pacientes con artritis reumatoidea. Enfatiza el autor que esta lesión es más frecuente de lo que creemos y que por lo tanto los pacientes que están recibiendo esta droga deben ser evaluados periódicamente por un oftalmólogo. Nos solidarizamos con este modo de pensar del Dr. Buxeda y a continuación pasamos a citar algunos datos importantes sobre el mismo tema.

Como recordarán los lectores durante la Segunda Guerra Mundial los antipalúdicos previamente usados, la quinina y la quinacrina fueron reemplazados por productos sintéticos derivados de 4-amino-quinolina, parientes químicos de los alcaloides de chinchona. En 1951 Page (1) mientras trataba 18 pacientes de lupus discoide con mepacrina observó una mejoría notable en una artritis reumatoide que tenía uno de ellos. Basándose en esta observación varios investigadores comenzaron a usar estas drogas en el tratamiento de la artritis reumatoidea y en 1957 Bagnall (2) reportó una mejoría notable en un 70% de una serie de pacientes con esta enfermedad tratados durante 4 años. Desde entonces han sido muchos los informes que provienen de distintas partes del mundo y que comprueban la eficacia de las mismas en el tratamiento de algunos casos (entre un 30 y un 70 por ciento) de artritis reumatoidea y en lupus eritematosus. Meredith, Villalobos y Lackington (3) reportan también sobre su efectividad en un por ciento alto de casos de osteoartritis y reumatismo. En octubre de 1962 y en el "Bulletin on Rheumatic Diseases" Mainland y Sutcliffe (4) reportan los hallazgos en un estudio a ciegas que se llevó a cabo por el comité de clínicas cooperativas del "American Rheumatism Association" presidido por el Dr. Charles Ragan y donde encuentran que usando varios métodos de evaluación objetiva había una diferencia significativa de el efecto de estas drogas en el tratamiento de la artritis reumatoide cuando se comparaba con el efecto de placebo.

La cloroquina fue sintetizada independientemente en Alemania y en los Estados Unidos durante la Segunda Guerra Mundial. Es de fácil absorción intestinal y tiene una afinidad marcada por las nucleoproteínas de tal manera que se fija fácilmente a la célula concentrándose en ciertos órganos especialmente en hígado, riñón y bazo. También se deposita en grandes cantidades en los tejidos

del ojo que contienen melanina tales como el iris, el coroide y la retina en concentraciones mucho más altas que en el hígado (5). La eliminación de la droga es lenta y mayormente por el riñón, pudiéndose encontrar presente en la orina en pequeñas cantidades varios años después de descontinuarse su uso.

Entre otros sus efectos farmacológicos son: 1. inhibición de la adenosintrifosfatasa con economía de ATP, 2. vasodilatación coronaria, 3. disminución de la aglomeración intravascular patológica de hematies, 4. bloqueo "in-vitro" del fenómeno de L.E., y 5. aplanamiento de ondas T en el E.C.G. de sujetos sanos. El efecto terapéutico de estas drogas es polifacético siendo efectivas en infecciones por protozoos tales como la malaria, la amebiasis y giardiasis. Se usa en las enfermedades reumáticas, en arritmias cardiacas, angina de pecho, dermatitis, etc.

Los efectos tóxicos de estas drogas se observan con mayor frecuencia en aquellas situaciones donde su efecto terapéutico requiere el uso prolongado de las mismas y especialmente cuando se usan dosis altas. Hay un sinnúmero de efectos secundarios que incluyen picor, erupción de piel, dolor de cabeza, dolor abdominal, náusea, anorexia, diarrea y fotofobia. Muchos de estos se observaron casi con igual frecuencia en los pacientes que recibían placebo en el estudio del Comité del "American Rheumatism Association" (4), y por lo tanto no siempre pueden atribuirse a la droga.

Los efectos tóxicos de mayor importancia clínica, como nos refiere el Dr. Buxeda en su carta, son las afecciones oculares. Estos se pueden dividir en 2 grupos: las keratopatias y las retinopatias. Los cambios corneales asociados con la cloroquina fueron descritos por primera vez en 1958 por Hobbs y Calnan (6) y por Calkins (7). Finos depósitos de la droga y/o sus metabólitos se observan en el epitelio corneal. Estos cambios son bastante frecuentes y ocurren en un 30 a un 70 por ciento de los pacientes bajo tratamiento. No existe una relación directa con la dosis ni la duración de tratamiento. Estos cambios tienden a desaparecer gradualmente una vez se descontinúa la droga. Un 50% de los casos así afectados desarrollan síntomas que consisten de halos, fotofobia y visión borrosa. No es necesario descontinuar el tratamiento a menos que los síntomas visuales sean severos (5).

De mucha más importancia son los efectos tóxicos de la cloroquina y sus parientes químicos en la retina. Hobbs, Sorsby y Freedman (8) en 1959 fueron los primeros en notar estos cambios describiendo degeneración de la retina en 4 pacientes que tomaron la droga por espacio de varios años. El primer estadio o etapa de la retinopatía se limita a cambios en la macula y consiste de edema, gra-

nulación anormal, depigmentación en parches y proliferación del epitelio de pigmento dando la apariencia de un defecto circular en la macula. En el estadio moderado ya hay extensión de los cambios a los cuadrantes temporales superiores imitando en los campos visuales una hemianopsia bitemporal. En el estadio avanzado prácticamente puede estar envuelto todo el campo visual con pérdida total de la visión. Con los cambios en la macula se altera también la identificación de colores. Las pruebas electrofisiológicas del electroretinograma (RG) y del electro-oculograma (EOG) también son alteradas.

Estudios de la distribución de cloroquina e hidroxycloroquina demuestran que estas drogas se depositan mayormente en aquellos tejidos del ojo que contienen melanina, el iris, el coroide y el epitelio pigmentado de la retina y se cree que esto explica el desarrollo de la retinopatía. Esto se ha notado que ocurre también con otras drogas habiendose informado en 1962 con fenotiazida (5) y produciéndose con esta droga una retinopatía muy similar a la de cloroquina. Hay autores que opina que el tratamiento previo de estos pacientes con fenotiazia y sales de oro los predispone a desarrollar retinopatía al ser tratados con cloroquina.

La incidencia de retinopatia por cloroquina que ha sido reportada por distintos autores es muy variable. Scherbel, Mackenzie, Nousek y Atdjian (9) encontraron sólo 2 casos en una serie de 408 pacientes que habían estado recibiendo tratamiento entre uno y nueve años. La dosis que ellos usaron es de 250 mg diarios de cloroquina o de 400 mg de hidroxicloroquina en el adulto y la mitad de esta en niños sobre 50 libras de peso. Por otro lado Henkind y Rothfield (10) reportan 6 casos en una serie mucho más pequeña pero todos estos tomaron 500 mg de cloroquina por un período de tiempo de 6 meses a 7 años. Todos los investigadores están de acuerdo en que la incidencia de rerinopatia guarda una proporción directa con la dosis que se use y con la duración de tratamiento aunque el factor más importante parece serla dosis. Aunque se han descrito cambios tempranos que revirtieron al dejar el tratamiento, la moyoría de estos son permanentes y he aquí la importancia de esta condición.

El uso de drogas en el tratamiento de cualquier enfermedad conlleva un riesgo. Quizás este es aún mayor cuando el uso de la droga es necesario por períodos prolongados de tiempo como ocurre en el tratamiento de enfermedades crónicas como la artritis reumatoidea y ellupus eritematosus. Mas aún en muchas ocasiones el paciente continúa autoterapia una vez se siente mejor y deja de visitar al médico. No es infrecuente la situación en que el paciente se olvida o mal como en el caso de estas drogas, catastrófico.

Personalmente creo se deben tomar las siguientes precauciones en el uso de estas drogas en el tratamiento de enfermedades reumáticas.

1. Usarla en aquellos pacientes que presentan un cuadro clínico que aunque posiblemente se deba a artritis reumatoidea pudiesen ser casos de lupus eritematosus. Para aquellos pacientes con artritis reumatoidea clásica se prefiere el uso de sales de oro, ya que son más efectivas y obligan a seguir más de cerca al paciente.

2. No se deben usar en pacientes con lupus excepto en aquellos con enfermedad sub-aguda y que no tengan nefritis severa, leukopenia o anemia severa ni trombocitopenia.

3. Antes de comenzar la administración de la droga se debe hacer una evaluación oftalmológica incluyendo examen minucioso de la córnea y de la retina y de los campos visuales, y este debe repetirse periódicamente, a los 6 meses y luego cada 3 meses mientras se continúe el tratamiento.

4. Nunca se debe usar una dosis mayor de 250 mg de cloroquina o de 400 mg de hidroxycloroquina al día en adultos y la mitad de la misma en niños de interpreta las instrucciones del médico. El resultado de estas situaciones puede ser, más de 50 libras de peso, y se debe descontinuar la droga a la primera indicación de retinopatía.

Russell A. Del Toro, MD, FACP

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AUTO-EVALUACION

Como resultado del ímpetu que ha recibido la investigación médica en los últimos años, el caudal de conocimientos en todas las ramas de la medicina y las ciencias asociadas ha venido aumentando con rapidez vertiginosa. Se ha estimado que esta producción de conocimientos nuevos dá lugar a que se reemplace en un cincuenta por ciento cada cinco años. Para el médico individual y para aquellos que están envueltos en la educación médica, es fuente de gran preocupación la eficacia con que pueda la profesión asimilar este enorme acopio de material científico y hacerlo llegar al lecho del enfermo para su beneficio. Corremos todos el riesgo, si no tomamos medidas vigorosas, de encontrarnos completamente rezagados.

Personas conscientes de este problema han llegado a sugerir que a intervalos regulares se le exija al médico, para continuar en su profesión, una recapacitación en el campo de su práctica. No vislumbramos la aceptación de tal sistema en nuestro medio.

Dentro del marco individualista que caracteriza nuestra profesión, la responsabilidad por la educación continuada queda en manos del médico mismo. Las sociedades médicas y las escuelas de medicina siempre han aceptado como una de sus más importantes funciones el proveer facilidades para la educación post-graduada. Los editores de publicaciones médicas también han compartido esta responsabilidad. La numerosa asistencia de médicos a los congresos de las diversas sociedades y a cursos post-graduados y la vasta circulación de las revistas médicas atestiguan la aceptación de esta obligación por lo menos por una fracción importante de la profesión. La efectividad de los presentes métodos de educación post-graduada, sin embargo, nunca ha sido evaluada adecuadamente. Es también a menudo difícil para el médico individual evaluar sus propias necesidades educacionales y el escoger, dentro del material a su alcance, aquello que es de valor duradero o de aplicación práctica.

Probablemente preocupados con estos problemas y siempre atentos a las necesidades de la educación médica, los dirigentes del American College of Physicians han introducido una innovación cuyas repercusiones son difíciles de predecir. Sobre una base voluntaria los miembros de esta distinguida sociedad se han sometido a un examen general (1) que trata de abarcar las áreas más importantes del extenso campo de la Medicina Interna. Se trata de una auto-evaluación, siempre difícil, de sus conocimientos. Los resultados de la prueba son sólo para

su propia ilustración. El examinado se entera de sus fallas y se le sugieren lecturas específicas para corregir sus deficiencias.

La información obtenida de este tipo de evaluación podría servir de guía para la estructuración de futuros programas post-graduados para grupos específicos de médicos.

La efectividad de este ejercicio queda aún por evaluarse, pero todos los interesados en la educación médica esperamos con interés los resultados de este novel experimento.

Julio V. Rivera, M. D.

Reference

1) Medical knowledge self-Assessment Program Bulletin American College of Physicians, 9:2, 1968.

ACTUALIDADES MEDICAS

Fertility and Educational Attainment Puerto Rico, 1962

One of the serious gaps in birth statistics for the United States is information on the socio-economic status of the parents. It is accurately known how many children are born and the age, race, residence, and other characteristics of their parents. But no ready index of their socio-economic standing exists. Hence, it is difficult to make meaningful statements about the quality of the social environment in which children are born and raised and to determine how rapidly certain important segments of our population are growing.

.....

For several reasons, the use of "educational attainment of parents" on the birth certificate has been proposed as an alternative to "father's occupation" as an index of socioeconomic status. A number of recent interview surveys show that the parents' education (most tabulations use that of the mother) is more closely related to fertility variables (number of children ever born, spacing of births, and effectiveness in controlling pregnancy, for example) than any other single measure of socio-economic status, such as father's occupation. father's income, and family income.

.....

For these reasons, the latest revision of the U. S. Standard Certificate of Live Birth (recommended for adoption by all registration areas as of January 1, 1968) asks for the educational attainment of the mother and the father and does not include any item on father's occupation.

Even before it was decided to add educational attainment to the standard certificate, two registration areas independently added the item to their certificates. Minnesota did so in 1965 and Puerto Rico in 1962. In this report, Puerto Rican data for 1962 are used to illustrate the uses of data on educational attainment. In the future, it may be possible to make similar analyses for the entire United States.

Differences in family size associated with educational attainment have been frequently noted in Puerto Rico. All evidence points to an inverse differential: fewer children are borne by women with more education than by women with less education.

The proportion of women who have ever married varies with educational attainment in Puerto Rico. According to the 1960 census, for example, among women aged 35-44 years, the proportion ever married was 85 percent for those with 9 years or more of school compared with 91 percent for those with less school. Rates based on all women, therefore, exaggerate the higher fertility of the less-educated.

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Proportionately fewer of the Puerto Rican women of high educational attainment marry than those of lesser educational attainment. Among the married giving birth in a particular year, the less-educated have married at relatively young ages, have had several children, and as a consequence

give the illusion of a relatively slow pace of childbearing. The better-educated, in contrast, have married at older ages, are childless or have borne very few children, and as a consequence are having their births relatively soon after marriage. Proportionately fewer of these better-educated women go on to have more children in future years and, consequently, their completed fertility is relatively low.

.....

There are two types of marriage in Puerto Rico. One is legal marriage, in which the couple is married formally in a civil or religious ceremony. The other is consensual marriage, in which the couple lives together in an informal union under common law. Approximately three-fourths of all parents of children born in 1962 were legally married, while one-fifth were consensually married. When added together, both types of marriage accounted for 96 of every 100 births.

This means that about 4 out of every 100 births were illegitimate. Table 5 shows that this percentage varies considerably according to the age and educational attainment of the mother. Although the percentage of births to unmarried mothers declines with age, it also declines with educational attainment.

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The percentage of births to consensually married mothers also declines with education. Below the ninth-grade level, about 1 in every 3 to 4 births occurs to consensually married couples. Where the husband and wife are of different educational levels, the percentage of consensually married diminishes as the education of either spouse rises. Childbearing in a consensual union is largely a phenomenon of the lower educational classes.

.....

This report illustrates some of the uses of data obtained from birth certificates on the educational attainment of parents. Data on births in Puerto Rico in 1962 are presented here, but similar studies are projected for other birth registration areas of the United States. Later studies may go well beyond the limits of the present study, especially when data for a series of years and different areas become available.

In this report data on education reported on the Puerto Rican birth certificate have been used for two purposes: first, to examine the differential fertility rates of socioeconomic groups in a calendar year, and, second, to describe differences, which are associated with socioeconomic class, for characteristics relevant to birth.

The data indicate certain advantages for those children fortunate enough to be born into high social classes. The advantages of beginning life with a desirable birth weight, few siblings, legally married parents, and a metropolitan residence favor the newborn infant in the better-educated classes. Puerto Rican children beginning life with less-educated parents have disproportionately high frequencies of immature and postmature birth weights, illegitimacy rates, and large numbers of siblings with whom to share the limited family resources.

Reproduced from Vital and Health Statistics, Public Health Service Publication No. 1000 - Series 21 - No. 12.

NOTICIAS

Locales

ASAMBLEA SEMIANUAL

La Junta Directiva de la Asociación Médica de Puerto Rico, con la cooperación de la Sociedad Médica del Distrito Occidental, celebrará la Asamblea Semianual de la Asociación durante los días 4 al 6 de julio de 1968, en Mayagüez.

El Consejo Científico desea la cooperación de la matrícula con la aportación de trabajos científicos para presentarse el 4 y 5 de julio. Se pueden preparar paneles o presentaciones individuales de veinte minutos.

Exhortamos que los que desean presentar trabajo lo comuniquen con la mayor brevedad posible, y preferiblemente antes del 15 de abril de 1968, al Presidente del Comité de Programación Científica.

NEW BOOKS

Other books received by the University of Puerto Rico School of Medicine and School of Dentistry.

Skeletal System

1. Adams, John Crawford. Outline of orthopaedics. 5th ed. Baltimore, Williams & Wilkins, 1966.
2. Flatt, Adrian E. The care of the rheumatoid hand. With foreword by Russell L. Cecil. Saint Louis, Mosby, 1963.
3. Frazer, John Ernest Sullivan. Anatomy of the human skeleton. 6th ed. Boston, Little, Brown, 1965.
4. Hollander, Joseph Lee. Arthritis an allied conditions. 7th ed. Philadelphia, Lea and Febiger, 1966.
5. Milch, Robert Austin. Surgery of arthritis. Baltimore, Williams and Wilkins, 1964.
6. Shands, Alfred Rives. Handbook of orthopedic surgery. 7th ed. Saint Louis, Mosby, 1967.

Cardiovascular System

1. Abramson, David Irvin. Circulation in the extremities. New York, Academic Press, 1967.
2. Baroldi, Giorgio. Coronary circulation in the normal and the pathologic heart. Washington, D.C., Office of the Surgeon General, Department of the Army, 1965.
3. Borell, Ulf Soren Mendelsson. The diagnosis of hydatidiform mole. Springfield, Ill., C. C. Thomas, 1966.
4. Burch, George Edward. A primer of electrocardiography. 5th ed. Philadelphia, Lea & Febiger, 1966.
5. Guntz, Marcel. Les veins sus-hepatiques. Alger, Laboratoire d'Anatomie, Faculté de Medicine d'Alger, 1959.
6. Norman, John C. Cardiac surgery. New York, Appleton, 1967.

NACIONALES

AMA ESTABLISHES APPROVAL PROGRAM FOR CERTIFIED LABORATORY ASSISTANTS

The American Medical Association's Council on Medical Education has established, in cooperation with the American Society of Clinical Pathologists, an approval program fr certified laboratory assistants

It is the ninth health occupation for which the AMA now maintains approval programs to assure that training standards acceptable to the medical profession are being met.

Before the AMA established the approval program last December, schools for certified laboratory assistants were approved only by the American Society of Clinical Pathologists.

The original certification program, aimed at providing standardized training and national certification under medical auspices, was initiated in 1963 by the ASCP and the American Society of Medical Technologists.

Upon completing an accredited 12-month course of hospital or laboratory school training and passing an examination, graduates are designated as certified laboratory assistants. To meet the increased demands for laboratory service, it is estimated that 100,000 certified laboratory assistants will be needed by 1975.

The current list of AMA—approved schools for laboratory assistants, as well as lists of other AMA —approved or acredited schools—cytotochnology, inhalation therapy technician, medical record librarian, medical record technician, medical technology, occupational therapy, physical therapy and x-ray technology—may be obtained by writing the AMA's Department of Allied Medical Professions and Services.

A six-page pamphlet, "A Career for You as a Certified Laboratory Assistant," may be obtained by writing the Secretary, Board of Certified Laboratory Assistants, 445 N. Lake Shore Drive, Chicago, Illinois 60611.

IIIrd INTERNATIONAL CONGRESS OF PHLEBOLOGY

Amsterdam, 9 - 13 September 1968

Congreso de Neurocirugía. — Toronto, Canadá; 25-28 setiembre 1968; (Dr. John R. Russel, 1815 Capitol Ave., Indianápolis 46202, EE. UU.).

IX Congreso Latino-Americano de Angiología. I Congreso Peruano de Angiología. — Lima Perú; 4-9 octubre 1968; (Dr. Carlos Forno, Apartado 702, Lima, Perú).

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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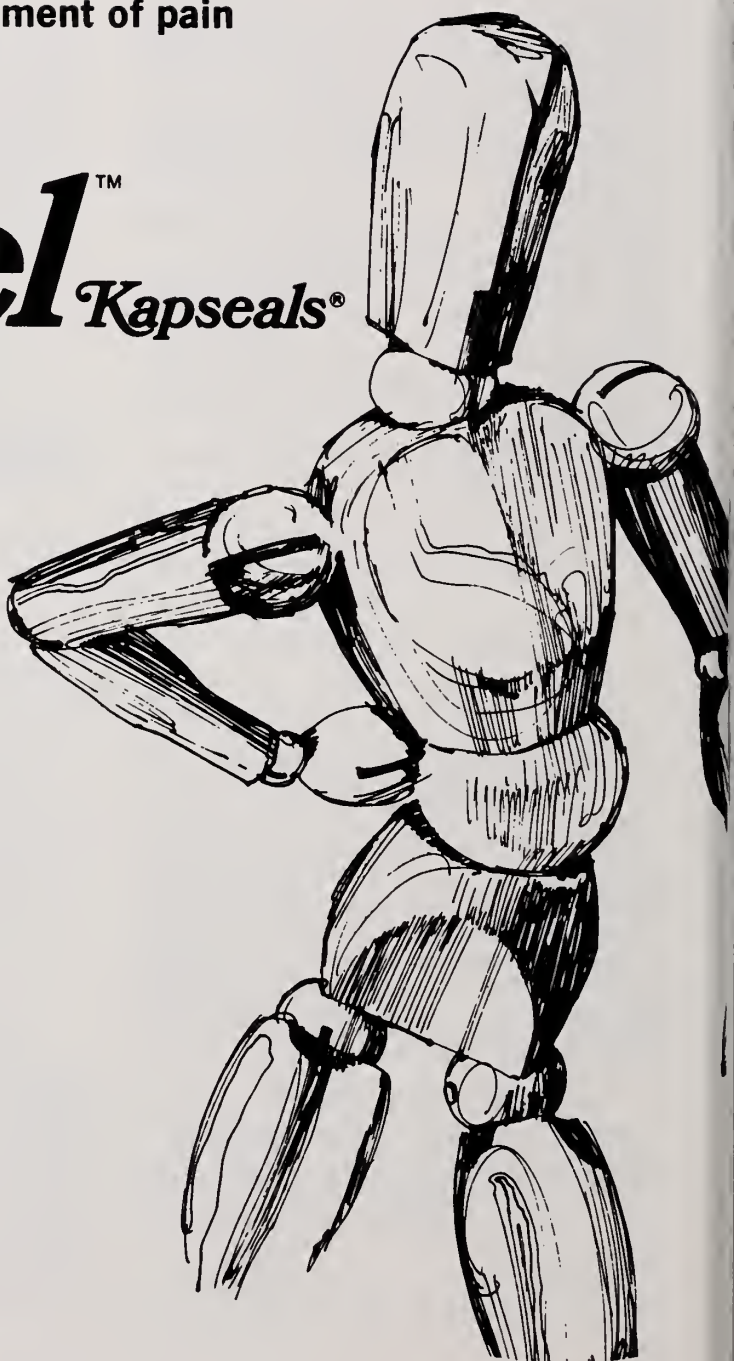
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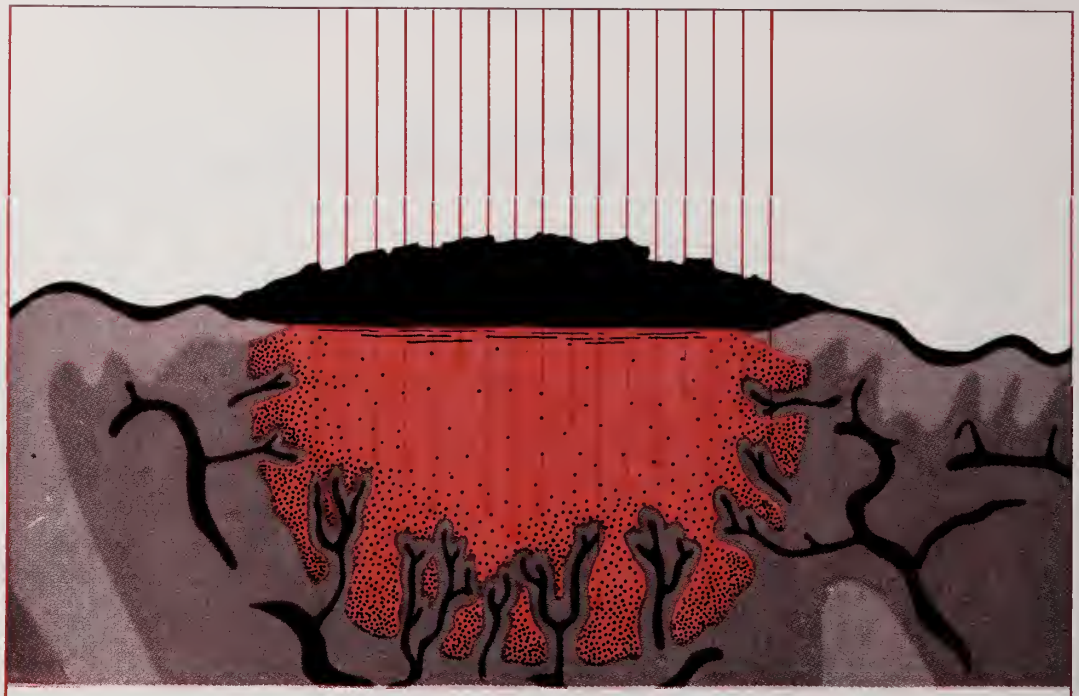
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COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

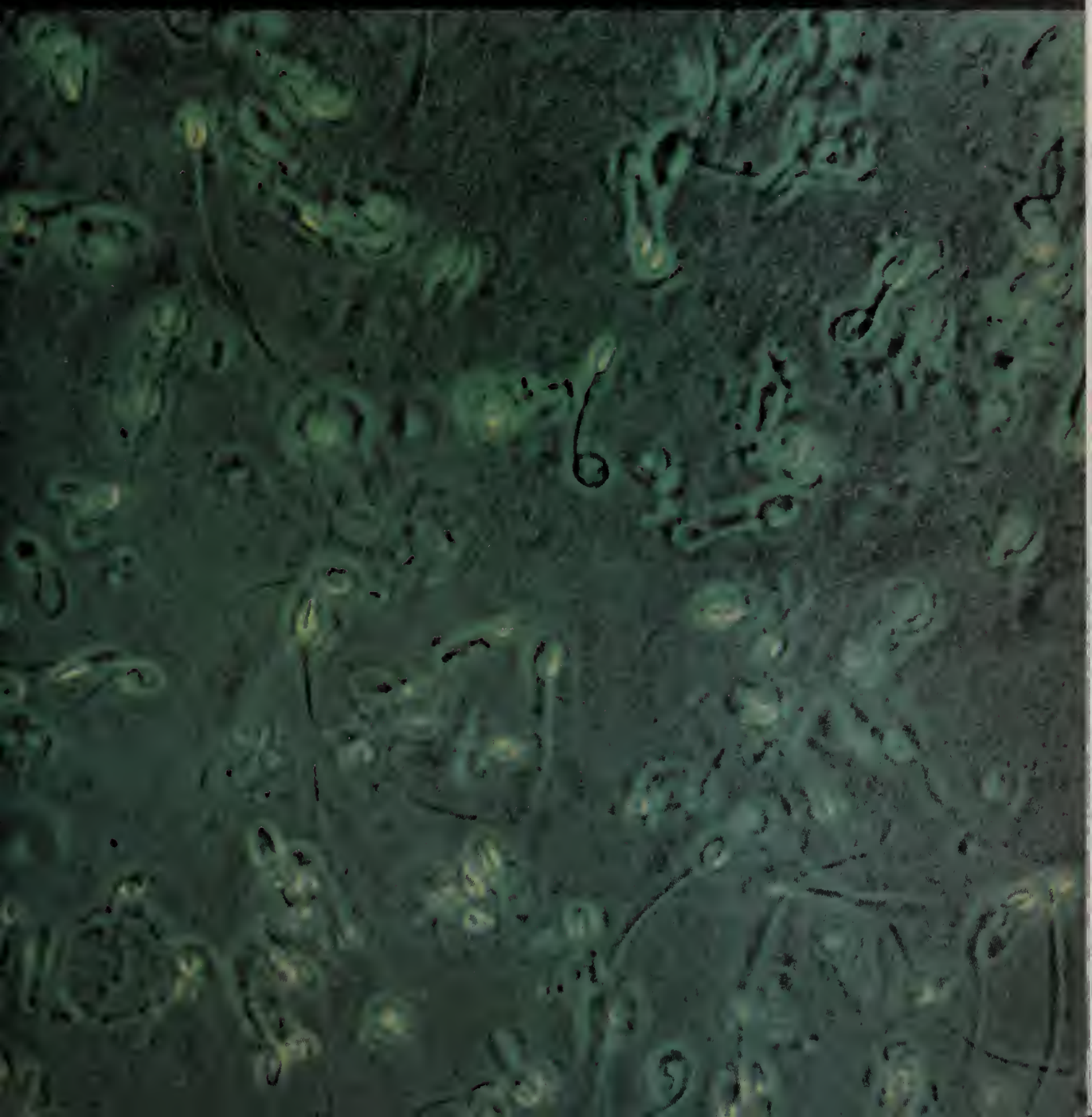
CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

When the talk turns to oral contraceptives, it makes medical sense to remember low-dose Norinyl®-1.

(norethindrone 1mg. & mestranol 0.05mg.)

Turn page for contraindications, precautions and side effects.



Reduction of oral contraceptive dosage to the lowest effective levels is a well-accepted principle of conservative medical practice. In keeping with this view, Norinyl is now also available as Norinyl-1, containing exactly one half the previous dosage of norethindrone and mestranol. Clinical experience has established that effective fertility control can be achieved with the same degree of reliability and safety with new Norinyl-1 when taken as directed.

What about switching patients from higher dosage forms?

In transferring patients to low-dose Norinyl-1 from higher-dosage oral contraceptives, some breakthrough bleeding may occur in the early cycles. In the majority of cases the bleeding episode is mild and self-limited. The long-term advantages of the lower dosage form should be weighed against the inconvenience of possible breakthrough bleeding in the individual patient.

Contraindications: 1. Patients with thrombophlebitis or with a history of thrombophlebitis or pulmonary embolism. 2. Liver dysfunction or disease. 3. Patients with known or suspected carcinoma of the breast or genital organs. 4. Undiagnosed vaginal bleeding.

Warnings: 1. Discontinue medication pending examination if there is sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, medication should be withdrawn. 2. Since the safety of NORINYL-1 (norethindrone 1 mg. with mestranol 0.05 mg.) in pregnancy has not been demonstrated, it is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. 3. Detectable amounts of the active ingredients in oral contraceptives have been identified in the milk of mothers receiving these drugs. The significance of this dose to the infant has not been determined.

Precautions: 1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as a Papanicolaou smear. 2. Endocrine and possibly liver function tests may be affected by treatment with NORINYL-1. Therefore, if such tests are abnormal in a patient taking NORINYL-1 it is recommended that they be repeated after the drug has been withdrawn for two months. 3. Under the influence of estrogen-progestogen preparations, preexisting uterine fibromyomata may increase in size. 4. Because these agents may cause some degree of fluid retention, conditions that may be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation. 5. NORINYL-1 should be used with caution in patients with a history of cerebrovascular accident. 6. In relation to breakthrough bleeding, and as in all cases of irregular bleeding *per vaginam*, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated. 7. Patients with a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree. 8. Any possible influence of prolonged NORINYL-1 therapy on pituitary, ovarian, adrenal, hepatic or uterine function awaits further study. 9. A decrease in glucose tolerance has been observed in a small percentage of patients on oral contraceptives. The mechanism of this decrease is obscure. For this reason, diabetic patients should be carefully observed while receiving NORINYL-1 therapy. 10. Because of the occasional occurrence of thrombophlebitis and pulmonary embolism in patients taking oral contraceptives, the physician should be alert to the earliest manifestations of the disease. 11. Because of the effects of estrogens on epiphyseal closure, NORINYL-1 should be used judiciously in young patients in whom bone growth is not complete. 12. The age of the patient constitutes no absolute limiting factor, although treatment with NORINYL-1 may mask the onset of the climacteric. 13. The pathologist should be advised of NORINYL-1 therapy when relevant specimens are submitted.

Side effects observed in patients receiving oral contraceptives: The following adverse reactions have been observed in patients receiving oral contraceptives: nausea, vomiting, gastrointestinal symptoms (such as abdominal cramps and bloating), breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, edema, chloasma or melasma, breast changes (tenderness, enlargement and secretion), change in weight (increase or decrease), changes in cervical erosion and cervical secretion, suppression of lactation when given immediately postpartum, cholestatic jaundice, migraine, rash (allergic), rise in blood pressure in susceptible individuals, mental depression.

Although the following side effects have been reported in users of oral contraceptives, no cause and effect relationship has been established: anovulation post-treatment, premenstrual-like syndrome, change in libido, changes in appetite, cystitis-like syndrome, headache, nervousness, dizziness, fatigue, backache, hirsutism, loss of scalp hair, erythema multiforme, erythema nodosum, hemorrhagic eruption, itching.

The following occurrences have been observed in users of oral contraceptives (a cause and effect relationship has been neither established nor disproved): thrombophlebitis, pulmonary embolism, neuro-ocular lesions.

The following laboratory results may be altered by the use of oral contraceptives: increased sulfobromophthalein and other hepatic function tests, coagulation tests (increase in prothrombin, Factor VII, VIII, IX and X), thyroid function (increase in PBI and butanol extractable protein-bound iodine, decrease in T^3 values), metyrapone test, pregnanediol determination.

norethindrone — an original steroid from

SYNTEX

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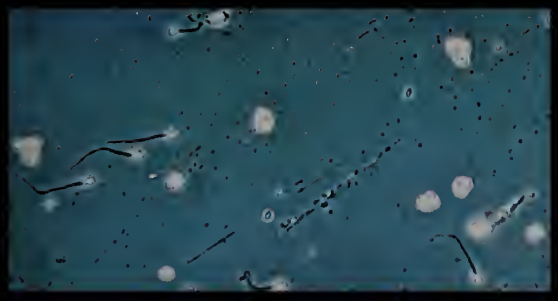
Here's why Norinyl-1 makes medical sense.

The effectiveness of Norinyl-1 as a low-dose oral contraceptive may be explained by its possible multiple action. In addition to its primary action of suppression of ovulation, Norinyl-1 may offer additional protective mechanisms... (1) creation of a cervical mucus that may be hostile to sperm penetration, and (2) development of an endometrium that may be out of phase with nidation. These effects are illustrated below.

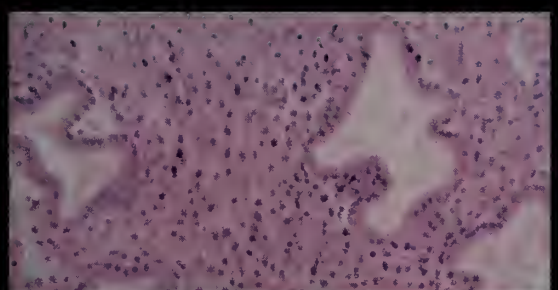
Untreated Patient



Cervical mucus at midcycle is usually thin and watery, with Spinnbarkeit (stretchability) of 15 to 20 cm.



Spermatozoa appear healthy, active, freemoving.

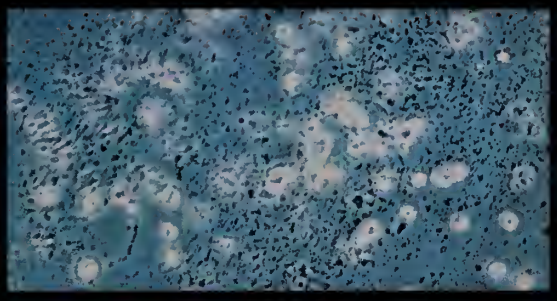


Endometrium of untreated patient is receptive to the fertilized ovum during secretory phase.

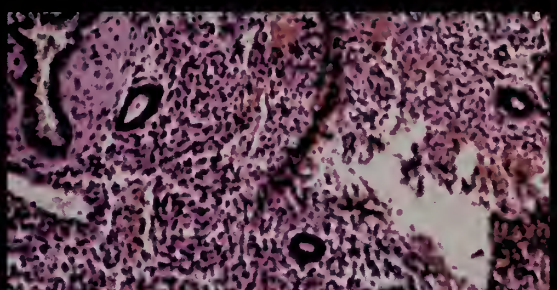
Norinyl-1 Patient



Cervical mucus at midcycle is scanty, viscous—with Spinnbarkeit of 1 cm. or less.



Immobile spermatozoa as they appear in cervical mucus taken from patient treated with Norinyl-1.



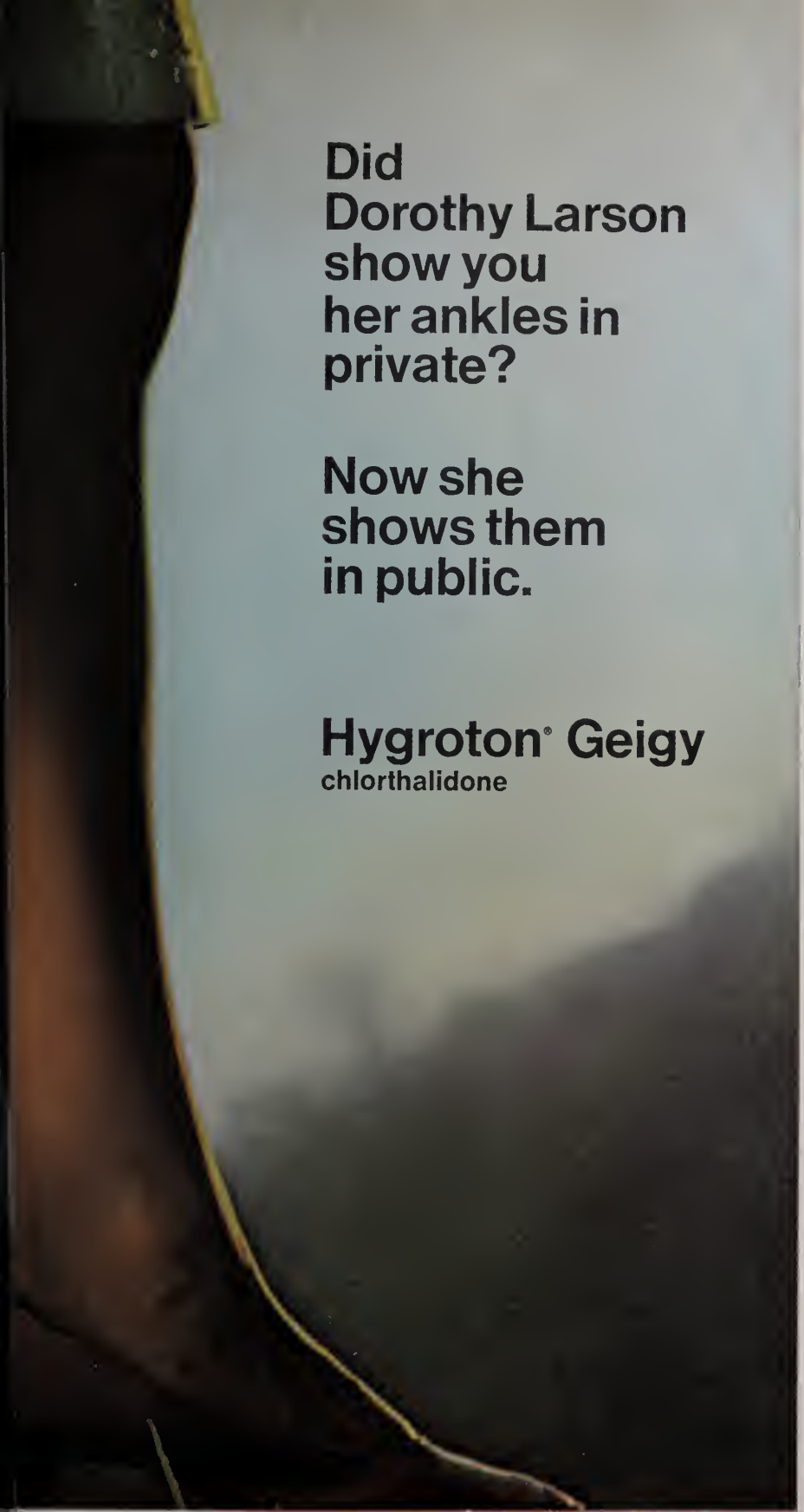
Norethindrone in Norinyl-1 accelerates secretory phase, suppresses glandular and vascular development.

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- new low dose of time-proved ingredients
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Indications: Hypertension and many types of edema involving retention of salt and water.
Contraindications: Hypersensitivity and most cases of severe renal or hepatic disease.
Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.
Use with caution in pregnant patients, since the drug may cross the placental barrier and adverse reactions which may occur in the adult (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn.
Precautions: Antihypertensive therapy with Hygroton should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents or other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Barbiturates, narcotics or alcohol may potentiate hypotension. Be
cause of the possibility of progr
sion of renal damage, perlodic
determination of the BUN is ind
cated. Discontinue if the BUN ri
or liver dysfunction is aggravat
Hepatic coma may be precipita
Electrolyte imbalance, sodium
or potassium depletion may oc
If potassium depletion should o
cur during therapy, Hygroton sh
be discontinued and potassium
supplements given, provided th



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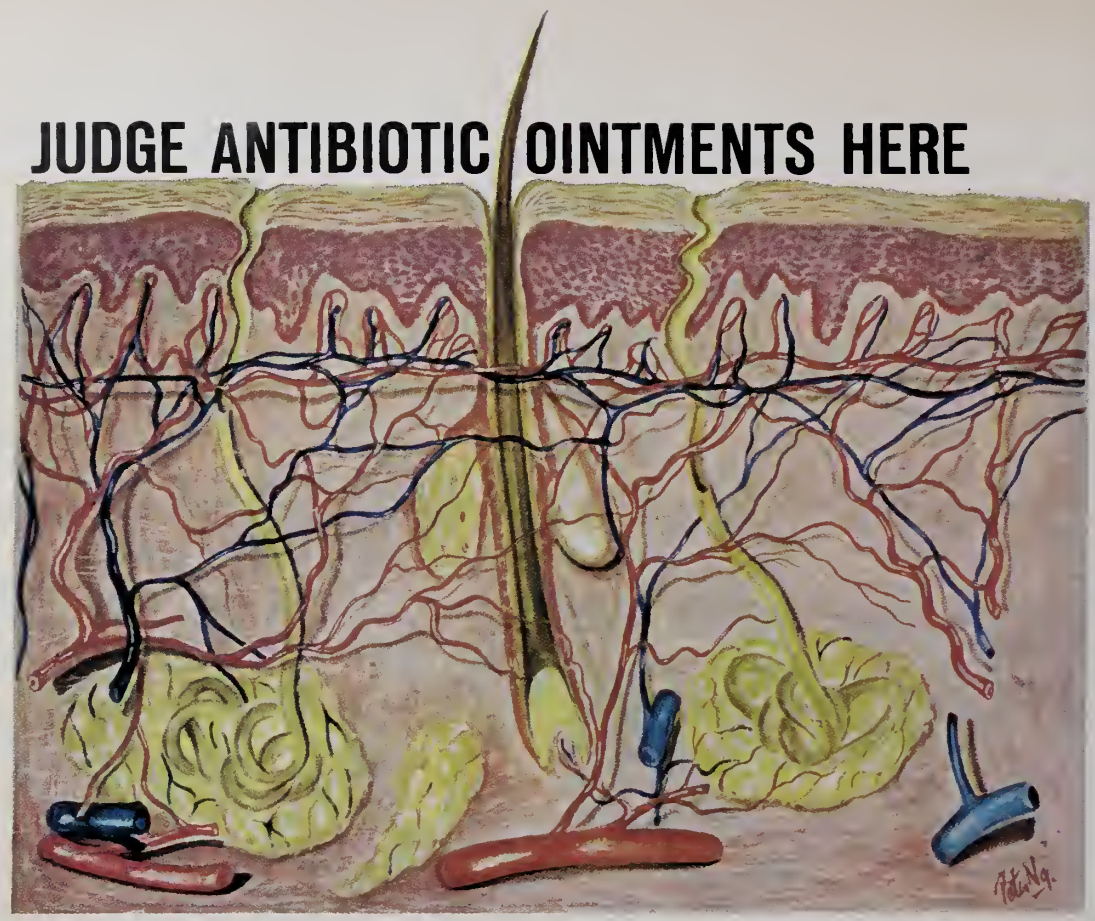
es not have marked oli-

cial care in cirrhosis or
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s receiving corticoste-
TH, or digitalis. Salt re-
s not recommended.
eactions: Nausea, gastric
vomiting, anorexia, con-
and cramping, dizziness,
, restlessness, hyperglyc-
peruricemia, headache,
amps, orthostatic hypo-
tension, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes, urticaria, purpura, necrotizing angiitis, acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.
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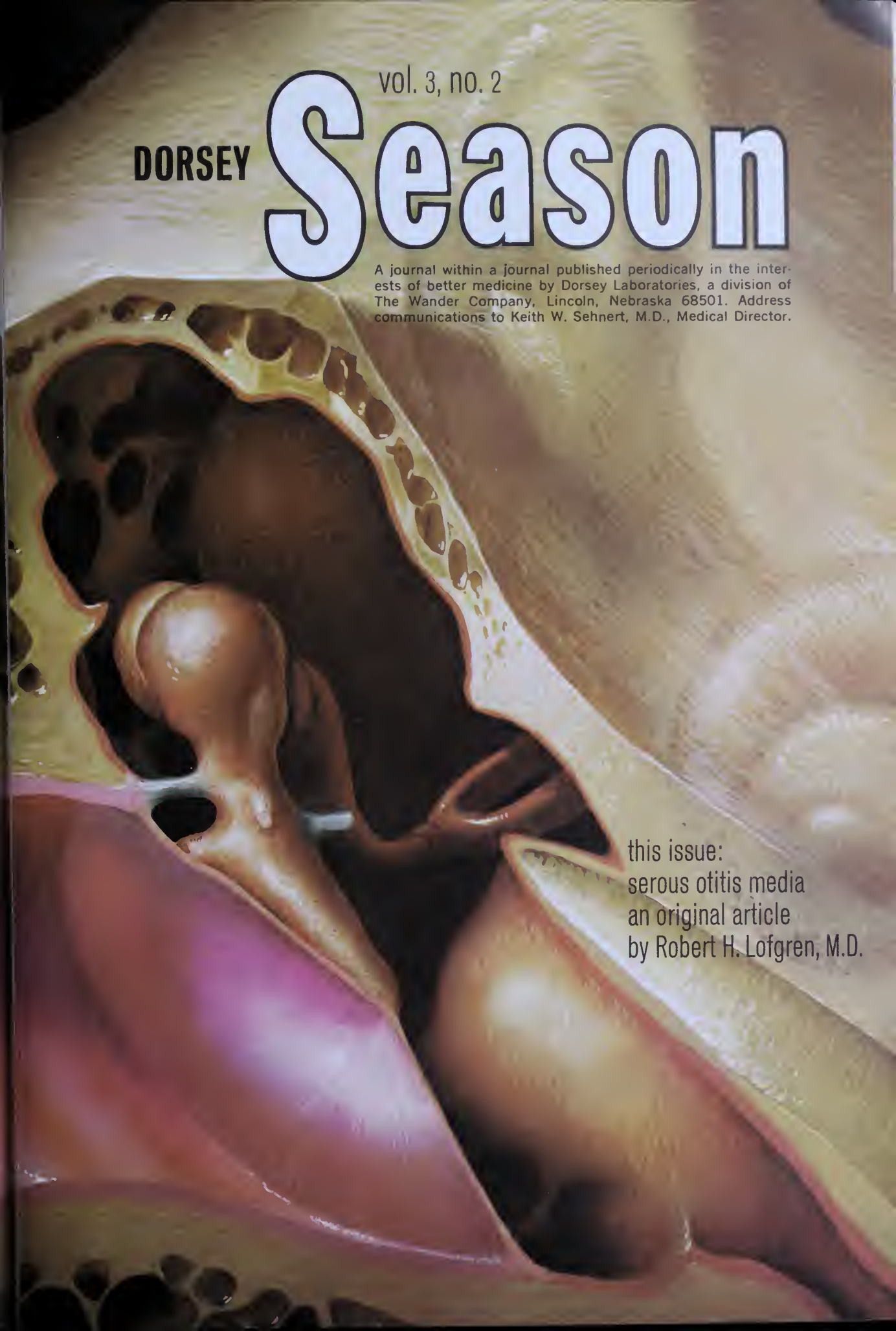
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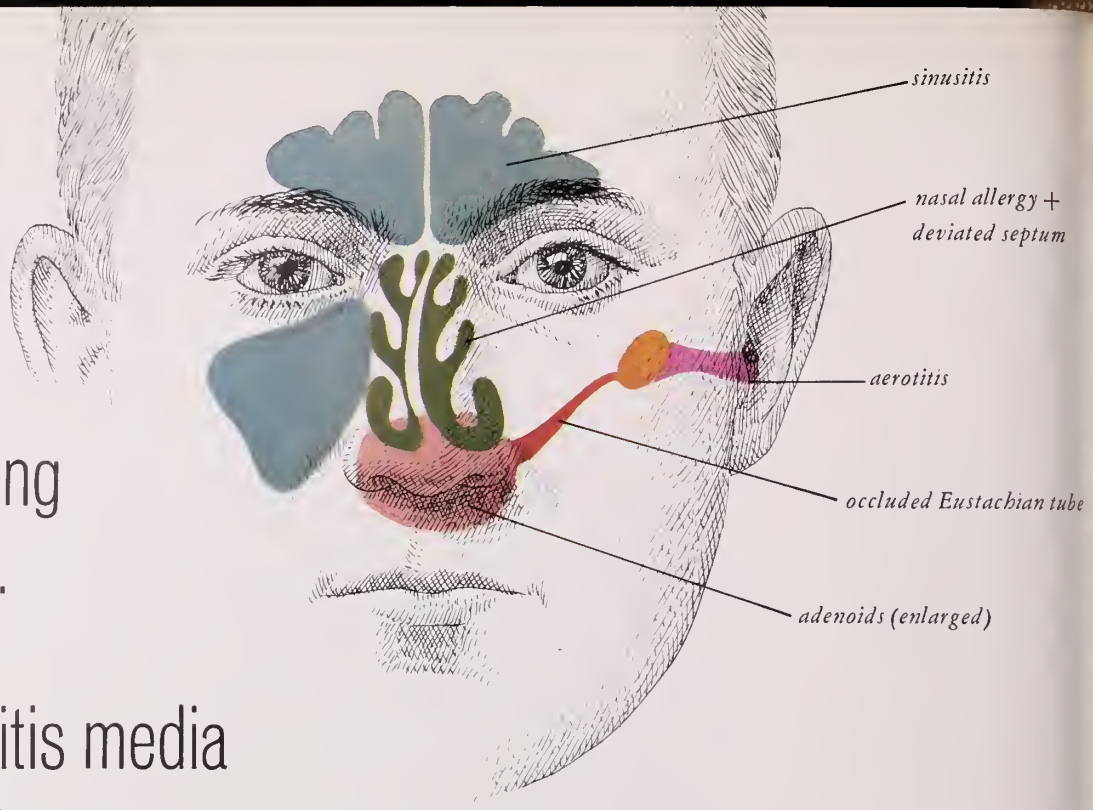
vol. 3, no. 2

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this issue:
serous otitis media
an original article
by Robert H. Lofgren, M.D.



the complaining earache... key to serous otitis media

Robert H. Lofgren, M.D.
Associate Surgeon, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts

Serous otitis media is probably the most common ear problem in children, especially in the wintertime. Diagnosis is usually easy in adults, but may be quite difficult in children, especially the very young child where one has to depend almost entirely on the physical findings.

The symptoms of serous otitis are a fullness in the ear, a mild hearing loss and mild earache. The earache can best be described as a "complaining earache" instead of a "screaming earache" as found in purulent otitis media. A young child may be irritable and pull at the ear. In milder cases, and as the ear recovers, gurgling and popping noises can be heard in the ear.

On examination one may see a yellow tympanic membrane and if a fluid level is present the diagnosis becomes easy. However, the eardrum may be dull gray, or slightly pink, or even perfectly normal. Pneumomassage using a Siegle otoscope or a closed-head electric otoscope must be done on both ears, otherwise the diagnosis will be frequently missed. Attempted movement of the drum with the pneumatic otoscope produces either a sluggish motion of the drum or no motion at all instead of the easily movable normal drum. The Rinne test is negative and there is a 15-20 decibel conductive hearing loss. The bone conduction may be better than normal and an air-bone gap may exist even with the air conduction within normal limits. Occasionally one finds a false nerve deafness on the audiogram when thick glue-like fluid causes immobility of both the oval and round window. Both conditions return to normal when the fluid is removed, but they make the interpretation of screening audiograms very difficult.

There is no single cause for serous otitis. One factor always present is blockage of the eustachian tube, but this alone is not enough to produce fluid. There must also be an inflammatory reaction. Blockage of the eustachian tube may be caused by many conditions. In children the most common cause is enlarged adenoids. In the summer the next most common cause is allergy. Upper respiratory infections or influenza are common causes in the winter. Nasal allergy, acute and chronic sinusitis, nasal septal deformity and cleft palate can all cause eustachian tube obstruction. Some children may have a congenitally small eustachian tube, but fortunately they usually "grow out of the problem."

The first sign of a nasopharyngeal tumor is often a serous otitis. One must always rule this out in any adult who later in life develops repeated or persisting serous otitis. Causes sometimes overlooked are nasogastric tubes after surgery, simple obesity and cardiorenal disease, which may produce congestion in the mucosal lining of the eustachian tube. In recent years we have been seeing a new cause—acute otitis media, where the patient is adequately treated with antibiotics but where drainage has not been

established either through the eardrum or down the eustachian tube. A sterile exudate is left in the middle ear.

The inflammatory response may be caused by a marked negative pressure as in air otitis from flying, or it may be from a mild bacterial or viral infection in the middle ear. Serous fluid is a good culture medium and will frequently go on to purulent otitis media, especially if the original blockage was caused by an infectious process such as acute rhinitis or adenoiditis. When the infection heals there may be scarring in the middle ear mucosa. Mucous glands develop in this tissue and pour out a thick mucoid material. This ear usually looks normal until a pneumatic otoscope is used. The objectives in treating serous otitis are to remove the obstructing agent and to provide drainage from the middle ear. Often this can be accomplished by decongestants and nose drops. If large obstructing adenoids are present they should be removed. Sinusitis should be treated with oral decongestants or nose drops, plus antibiotics where indicated. Nasopharyngeal tumors should be treated. Allergies should be treated with antihistamines and, where indicated, by desensitization.

If the fluid does not clear with medical treatment within a week or two, a myringotomy should be done. If there is a question of active infection or if the fluid looks purulent, as is seen at the conclusion of acute otitis, cultures are taken. On adults this can be done in the office without anesthesia. It is no more painful than an intravenous needle for a blood test. A good safe topical anesthetic has a tremendous psychological value to the patient. Children under the age of 1 require no anesthesia. Between the ages of 1 and 3 anesthesia is not absolutely essential although a general anesthetic may be used to avoid the child's possible mistrust at follow-up examinations. I usually do the myringotomy at the same time as the adenoidectomy if the adenoids are enlarged. Once drainage has been established with decongestants or by myringotomy, positive pressure inflation of the middle ear is invaluable in forcing out the serous fluid and keeping it from reforming. The patient can do this himself by performing the Valsalva maneuver. This should be done several times a day, by taking a deep breath, holding the nose and blowing hard against the closed lips for a second or two.

In resistant cases where the fluid reforms as soon as the myringotomy heals, small polyethylene tubes are inserted through the myringotomy site. Insertion of the tubes, even in adults, usually requires an anesthetic. Good anesthesia can be obtained by infiltrating the canal wall with a local anesthetic, using a #27 needle. Once inserted the patient has no sensation of the tubes' presence. Be careful to caution the patient or parents not to allow any water to get into the ear canal while a myringotomy is open or a tube is in place. Water can be kept out by a pledget of lamb's wool in the ear canal or a cotton pledget thickly coated on the outside with petroleum jelly. I check these patients a week after a myringotomy to be sure it is healed and at two month intervals until the tubes have fallen out, usually within three to six months after insertion.

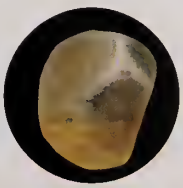
The mucoid type of fluid is so thick and tenacious that it is appropriately called a glue ear. It is aspirated only with difficulty through the eardrum, and occasionally must be removed through a tympanotomy. This thick, glue-like fluid is prone to recur, as the myringotomy usually heals long before the mucous membrane has returned to normal. Repeated myringotomies, as many as ten or twenty, were formerly required for this condition. Now polyethylene tubes are inserted initially when this thick, glue-like material is found. At times a subacute mastoiditis may accompany the serous otitis, which will necessitate a simple mastoidectomy before the condition can be eradicated. Usually the thin serous fluid readily responds to decongestants or to a myringotomy and removal of the eustachian tube obstruction. Occasionally, however, even serous fluid will repeatedly reform. For this, resection of the tympanic plexus of nerves which lies on the promontory of the middle ear has been carried out, as the tympanic branch of the glossopharyngeal nerve is the secretomotor nerve to the ear.

Failure to diagnose serous otitis is the most common cause of the recurrent, almost continuous otitis me-

Otoscopic Views



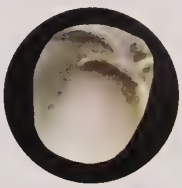
Normal



Acute Serous



Acute Purulent



Chronic Serous

dia seen in young children. In these cases a myringotomy will frequently provide a long-term cure without adenoidectomy or any other surgery. Failure to do this may allow the condition to go on to acute or subacute mastoiditis. Adhesive otitis media with scar tissue binding down the ossicles or tympanosclerosis may also result with permanent impairment of hearing. The prognosis for hearing with adhesive otitis or tympanosclerosis is usually poor. If the adhesions are removed, they reform, and the same is frequently true of tympanosclerosis even after a tympanoplasty. For many of these people a hearing aid is the only solution. The constant negative pressure in long standing serous otitis media may draw in either Schrapnell's membrane or the posterior superior portion of the eardrum forming a pocket to cause a chronic otitis media with cholesteatoma, which may not become apparent until twenty or thirty years later.

The non-medical complications of improper diagnosis or treatment may be even more serious. The irritable child, the frequent bouts of acute purulent otitis media with pain and fever, the expense of antibiotics and doctors, and the time lost from school or work affect the entire family.

In summary, serous otitis has many causes. There is a blocking of the eustachian tube and an inflammatory reaction in the middle ear mucosa, the latter usually caused by a mild infection. The treatment is to provide immediate drainage by decongestants and where necessary, by a myringotomy. The obstructing agent must be removed by surgery if it is adenoid or by oral decongestants, and antihistamines or nasal spray if it is an upper respiratory infection or allergy. Occasionally resistant cases require plastic tubes placed through the eardrum or other more radical surgery. Failure to treat properly leads to hearing loss which may be permanent, repeated acute otitis media or possibly even chronic otitis media with cholesteatoma.

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Side Effects: Moon face, acne, flushing of the face, buffalo hump, osteoporosis, spontaneous fractures, amenorrhea, aggravation of infection, psychic disturbances, thromboembolism, peptic ulcer, gastrointestinal hemorrhage, increased intracranial pressure, headache, insomnia, fatigue, purpura, hirsutism, vertigo, leukopenia, and increased intraocular pressure. Subcapsular cataracts may be formed on high dosages over long periods. A mild depression may occur. Necrotizing angiitis is rare. Ulcerative esophagitis and acute pancreatitis have occurred. Long-term administration results in definite catabolic effects, as indicated by negative protein and calcium balance. This catabolic effect coupled with anorexia may produce weight loss which is undesirable in some patients. A steroid myopathy with advanced muscle weakness may involve muscles of thighs, pelvis, and low back. Fluid and electrolyte balance differs from older corticosteroids in that it promotes mild sodium excretion. Patients with sodium retention and edema, either from underlying diseases or from previous therapy with other corticosteroids, will frequently lose weight and show increased urinary output associated with some sodium diuresis during the first 3 to 7 days of therapy. This effect will not be seen in patients with decreased glomerular filtration. Potassium balance is not affected under ordinary dosage circumstances; and potassium supplementation ordinarily is not necessary, unless the dosage exceeds 36 mg. per day for more than 14 days. Hypertension and edema are not commonly observed—they should not be used as indications of overdosage.

1. Lyons, J. A.: Treatment of Emphysema. *JAMA* 194:1234 (Dec. 13) 1965. 2. Riccitelli, M. L.: Modern Concepts in the Management of Emphysema in the Aged and Infirm. *J. Amer. Geriat. Soc.* 14: 497 (May) 1966.

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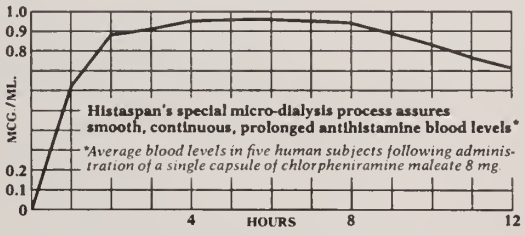
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El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

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INDOMETHACIN IN THE MANAGEMENT OF RHEUMATOID AND OSTEOARTHRITIC DISEASES

J. Soler-Bechara, MD

Prior to the introduction of corticotropin and cortisone in 1949 and 1950, an effective medical armamentarium against osteoarthritis and rhematoid arthritis was lacking, with the exception of salicylates for both of these disorders and gold salts for the latter.

However, the use of corticosteroids, potent and dramatic as they may be, is not justified in the great majority, if not all cases of degenerative joint disease; after years of experience and follow-ups they are now used sparingly, and for short periods, mostly in cases of rheumatoid (1).

Phenylbutazone, a non-steroidal inflammatory agent, came a few years later. Its use today in arthritic disorders is mostly confined to acute gout, acute bursitis and tenosynovitis since its possible toxic effects when used for periods of more than 2 or 3 weeks precludes its continued use without special precautions.

Hence, the need for a potent non-steroidal anti-inflammatory agent without the disadvantages of other antiarthritic drugs came to be fulfilled by indomethacin two years ago. It is now perhaps the most widely used agent, after aspirin, in osteoarthitis and rheumatoid arthritis (2, 3).

Indomethacin, chemically known as 1-(p — cholorobenzoyl) —5— methoxy —2— methylindole-3-acetic acid, a 3-indolyl acid derivative, is relatively insoluble in water but more readily so in organic solvents. It is well absorbed when given by mouth and, in the human, over a third of it is excreted by the kidneys as glucuronide in the first 4-6 hours (4,5) and the remainder within 24-36 hours. Radioactive tracer studies in man have confirmed that the ingested dose is rapidly absorbed to reach peak plasma level in about four hours with a half life of two hours (4,5).

This small study was conducted to further assess the effectiveness of indomethacin at the lower dosage levels, particularly in the setting of every day office practice as seen by a community rheumatologist.

It was decided to use this non-steroidal agent in general rheumatoid arthritic practice because of its several advantages:

1. an anti-inflammatory effect as evidenced by the rapid reduction of tissue swelling within two or three days of the onset of treatment; it is appreciably more active in reducing the swollen joints in active rheumatoid arthritis than in long standing cases (6, 7, 8, 11)
2. a marked analgesic effect quite distinct from the pain relief due to reduction of swelling (6, 7, 9); the effect is most marked in the pain of gout and osteoarthritis, somewhat less in rheumatoid arthritis.

3. an antipyretic effect, especially in the active stages of arthritis (8)
4. an absence of serious toxic effects seen so frequently with continued steroid and other non-steroidal treatments
5. since there is no evidence of agranulocytosis or other blood dyscrasias, treatment with indomethacin does not require the hematologic control necessitated by the use of pyrazolone derivatives

Materials and Methods

While no attempt has been made to make this a controlled study by using a double-blind technique, an accurate control of the response to treatment and to some extent of the course of the disease was possible by methodically scoring the presenting target symptoms throughout the period of treatement. The decision to start the patient on indomethacin was made solely taking in consideration the patient's welfare. They were followed at the intervals at which one would normally see a patient in private practice, depending on the severity of his illness and the time that was convenient to him to come for a return visit.

Most of the patients were previously on some other medication hence they were always asked to compare the present treatment (i.e., indomethacin) with their previous one. No concurrent treatment was given with indomethacin except for intra-articular steroids, when indicated. An objective evaluation by the physician was always made and laboratory studies were ordered only when deemed necessary and appropriate to assess the patient's illness or detect toxicity.

Dosage: The standard 25 mg capsule was used throughout the study, the patient being instructed to always take the medication with meals or with a full glass of milk. Treatment was commenced by administering 1-2 capsules per day, gradually increasing this dose by one 25 mg capsule after a period of a week or more.

Side Effects: In view of the many comments (2, 7, 8) in the literature on the high incidence of side effects and the precaution to be taken in the case of patients with history of peptic ulceration (10), a careful attempt was made to keep the patients on a minimal dosage consistent with comfort. They were not told about possible side effects when first given the medication but were asked if they felt any unusual symptoms since taking the medication. Patients with a history of peptic ulcer disease or even simple "heartburn" when taking aspirin were excluded from this study. In only one case was it necessary to stop the drug because of headache, although only 50 mg per day was administered.

Results

Twenty seven patients were studied. Nineteen had osteoarthritis of one or more joints, all proven clinically and by x-rays and eight had definite or classical rheumatoid arthritis using American Rheumatism Association criteria.

Ages of the patients with osteoarthritis ranged from 42 to 73 years with a mean of 59 years, and those with rheumatoid disease ranged from 34 to 66 years with a mean of 53 years.

The duration of illness before taking indomethacin in the patients with osteoarthritis ranged from 2 weeks to 14 years and in those with rheumatoid arthritis, 2 months to 10 years.

The number of patients in the two groups, the average daily starting and maintenance doses and the duration of treatment are summarized in Table I, together with the corresponding results obtained. Final results, i. e., the assessments of the clinical improvements after treatment was scored in the following manner: 0—worse, 1—no relief, 2—some relief, 3—moderate relief, 4—complete relief.

Twenty one percent (4 patients) of those with osteoarthritis reported complete relief of their symptoms. In all of these ex-

TABLE I: ARTHRITIS TREATED WITH INDOMETHACIN

Diagnosis	No.	Dosage (mg/day)		Treatment	Results			
		Initial	Maintenance	(months)	Excellent	Good	Fair	None
Osteoarthritis	19	75-100	50-75	7.5	4	7	7	1
Rheumatoid arthritis	8	75-100	50-75	6.0	2	1	2	3
Totals	27	—	—	—	6	8	9	4

cept one, the symptoms were of less than 2 months duration.

Moderate relief (i. e., almost complete relief of symptoms) was achieved by 68% (13 patients) of this group. The duration of illness prior to starting on indomethacin in this group was very wide; 6 months to 7 years, and they were followed from 4 to 14 months. It is of interest to note that in no instance was it necessary to give more than 100 mg of indomethacin daily and the average maintenance dose was 50-75 mg. daily.

Two patients (10%) with osteoarthritis reported some relief. One of these patients had severe bilateral hip joint disease of 14 years duration and he stated that indomethacin was the only medication that allowed him to be up and about.

The admittedly small group of patients (8) with rheumatoid disease did not fare as well. Three patients reported no relief at all and even felt that aspirin was as good or better than indomethacin (one of these three had been a gold therapy failure). Three reported some or moderate relief and are now using indomethacin instead of aspirin as the everyday analgesic and anti-inflammatory agent. The two patients who reported complete relief of their pain and inflammation had previously received corticosteroids; one of them is maintained on as little as 50 mg daily and develops severe arthralgias and synovitis of the knees if he discontinues the medication.

Undesired effects were quite infrequent in this small study, perhaps because the highest dose used was 100 mg per day. Severe pyrosis forced a 47 year old female patient to discontinue medication, and bothersome dizzy spells forced a 42 year old male to discontinue treatment. Three other patients complained of dizziness.

Mild headache and dizziness on 50-75 mg of indomethacin, not requiring discontinuation of the drug was reported by 4 patients. One patient reported tinnitus which stopped on lowering the dose of indomethacin and three reported mild pyrosis alleviated with antacids.

Conclusion

Indomethacin has come to fill a great need in the armamentarium against certain rheumatic diseases. When used in selected cases, as every medication should be, it will benefit at least 75% of patients, often for more than a year. It is not a substitute for any other medication or physiotherapy, but a welcome addition. Serious side effects need not be feared when moderate but therapeutically effective doses (75-100 mg daily) are used, in properly selected and well followed patients.

Resumen

La efectividad del anti-inflamatorio Indocin (indomethacin) se ensayó en 27 pacientes adultos, 8 de estos con artritis reumatoidea y 19 con artritis degenerativa. Todos fueron tratados por un promedio de 6.5 meses. Once de los 19 pacientes con osteoartritis reportaron alivio excelente o bueno de sus manifestaciones artríticas y 7 alivio moderado. Tres pacientes entre los de artritis reumatoidea tuvieron alivio excelente y uno alivio moderado.

Los efectos secundarios fueron pocos y reversibles al descontinuar el fármaco.

Se concluye que la indometacina, cuando es usada en pacientes seleccionados, es efectiva, segura y de gran utilidad en el armamentorio farmacológico del reumatólogo.

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BILHARZIA AND PATTERNS OF HUMAN CONTACT WITH WATER IN PUERTO RICO

William R. Jobin, ScD
E. Ruiz-Tiben, MSS

The patterns of human contact with natural surface waters in the tropics have a direct bearing on the transmission of bilharzia (schistosomiasis). It was the purpose of this study to determine the amount and frequency of water contact in Llanos Adentro, a rural burrough of Aibonito, Puerto Rico, to correlate this with the prevalence of bilharzia among the local population, and thus determine priorities for a control program to be based on prevention of human contact with infective waters.

The area studied was very hilly, on top of the central mountains of Puerto Rico, and 600 meters above sea level. The burrough of Llanos Adentro in the lower watershed of the Aibonito River has been known to be endemic for bilharzia since 1958 when it was incorporated into the Bilharzia Control Program of the Puerto Rico Department of Health in Aibonito (1, 2, 3). The pepole of Llanos Adentro live at a relatively low economic level for Puerto Rico, farming tobacco, coffee, and chickens.

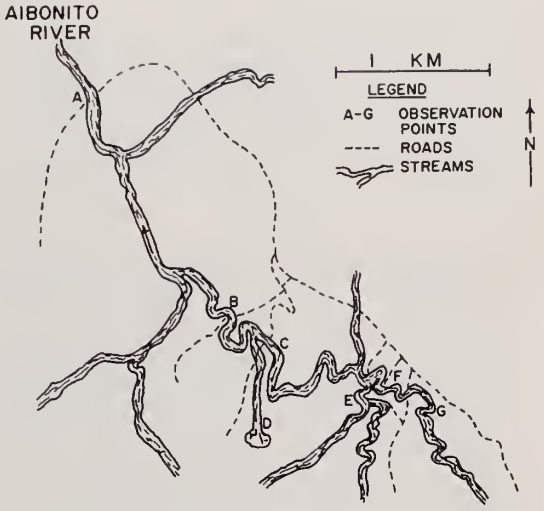


Fig. 1: Map of Llanos Adentro burrough of Aibonito showing the river and observation points for water contact survey.

Methods

In order to observe water contact, seven stations were selected by inspecting all waterbodies in Llanos Adentro and subjectively deciding where people would be most likely to come into contact with the water (Points A through G, Figure 1). For six consecutive days, observers remained at the seven stations, recording all evidence of water contact within their field of vision. In general the observers were at the stations from 10 A.M. to 3 P.M., probably the time of major water contact. The study lasted from Monday, October 10, 1966, through Saturday, October 15. Both Wednesday and Saturday were legal holidays;

This study was a joint effort of the Tropical Disease Section, Ecological Investigations Program, National Communicable Disease Center, Bureau of Disease Prevention and Environmental Control, Public Health Service, U. S. Department of Health, Education, and Welfare, and the Bureau of Vector Control, Division of Environmental Sanitation, Puerto Rico Department of Health, San Juan, Puerto Rico.

schools and government offices were closed. The time that the person entered and left the water was noted and the age of the individual was estimated. Those observed were kept unaware that water contact was being studied in order not to influence their behavior. The only still water body under observation was a farm pond, station D. The other stations were on the Aibonito River, with 1.30 kilometers under surveillance out of a total river length of 4.85 kilometers. The river discharge at the time of the study was about 10 liters per second.

As a means of determining the prevalence of bilharzia, stool examinations were repeated three times at one-week intervals on the school children of Llanos Adentro, grades 1 through 6 in the latter part of October. The stools were examined for schistosome ova by a formalinether certrifugation techniques. (4)

Results

During the six days of observation, 109 occurrences of water contact were observed at stations A, B, C, and D, involving 1,515 minutes of contact. However, at stations E, F, and G, no water contact was observed. Children of school age had the highest frequency of water contact (adjusted for age distribution of local population). Over twice as many contacts were observed as would be expected from the proportion of students in the local population (Table I). The ratio of observed contacts to expected contacts among preschoolers was low (0.5) probably because of the large number of infants in this age-group.

Students also had the longest exposure (adjusted) for any age group, with an observed/expected ratio of 2.1 (Table II). In this case the teenagers had the shortest adjusted exposure, and also had the shortest duration per contact, 5 minutes. However, prescholers, who had the expected amount of exposure for their age-group, had the longest duration per contact. Apparently only a few preschoolers went in the water, but they stayed an average of 35 minutes per contact compared to the average of 14 minutes per contact for the entire population.

Of the five classes of activity resulting in water contact, stream crossing occurred most often, 62 times, but it involved the shortest duration per contact, only 2 minutes (Table III). Clothes washing was observed only 4 times but the duration per contact was 76 minutes, the longest of any activity. In terms of total exposure, play activity ranked first with 773 minutes, followed in importance by clothes washing, bathing, stream crossing, and fishing, in that order.

There was slightly more water contact in the morning than in the afternoon, but no marked pattern was observed. Of the six days of observation, the rate of water contacts was 1.6 per hour on the two holidays, three times as high as the rate on the other days.

Results of the triple stool examinations indicated that the prevalence of bilharzia was highest among 9 and 10 year old children (Table V). The decrease in prevalence among older children indicated that the low water contact observed in teenagers may also have been true among 11 and 12 year olds. By the slope of the age-prevalence line, it is evident that 6, 7, and 8 year olds were at highest risk within the student age-group. Since the water contact study indicated the students were at highest risk among all the age groups, it is clear that the youger students, first and second graders, are the most important group for a program to prevent water contact in Llanos Adentro.

TABLE I: FREQUENCY OF HUMAN WATER CONTACT AS A FUNCTION AGE

Age Group	Pre-Schoolers	Students	Teenagers	Adults
Estimated Age (Years)	05	6-12	13-19	20+
Proportion of local population*	29.1%	15.2%	12.7%	43.0%
Observed distribution of 109 contacts	15	40	17	37
Expected distribution of 109 contacts**	31.7	16.6	13.8	46.9
Ratio of observed to expected frequency of contacts	0.5	2.4	1.2	0.8

**From census of 15 families living close to points of water contact.*

***Based on relative size of age groups, assuming frequency of contact is independent of age.*

TABLE II: DURATION OF HUMAN CONTACT WITH WATER AS A FUNCTION OF AGE

Age Group	Pre-Schoolers	Students	Teenagers	Adults	Total
Proportion in local population*	29.1%	15.2%	12.7%	43.0%	100.0%
Observed distribution of exposure to water, in minutes**	529	480	87	419	1,515
Expected distribution of exposure to water, in minutes	442	230	192	651	1,515
Ratio of observed to expected exposure to water	1.20	2.1	0.5	0.6	1.00
Number of contacts observed	15	40	17	37	109
Average duration per contact, in minutes	35	12	5	11	14

**Based on age-distribution of members of 15 families living close to points of water contact.*

***Based on relative size of age groups, assuming duration of contact is independent of age, and using total observed exposure of 1,515 minutes.*

TABLE III: NUMBER AND DURATION OF WATER CONTACTS

Activity	Number of Contacts	Total Duration of Contacts (Minutes)	Average Duration of Each Contact (Minutes)
Stream crossing	62	142	2
Bathing*	15	232	15
Clothes washing	4	305	76
Playing	24	773	32
Fishing	4	63	16
Totals	109	1,515	14

**Denotes people washing with soap.*

TABLE IV: AGE-SPECIFIC PREVALENCE OF BILHARZIA AMONG SCHOOL CHILDREN

	Positive Stool Samples/Total Examined				
Age	Oct 18 First Exam	Oct 25 Second Exam	Nov 1 Third Exam	Number of Positive Individuals from 3 Exams	Percent Prevalence
6	1/20	3/20	3/20	3/20	15.0
7	0/24	2/24	1/24	3/24	12.5
8	3/31	3/31	3/31	6/31	19.4
9	5/24	5/24	4/24	8/24	33.3
10	5/34	8/34	9/34	11/34	32.3
11	3/25	3/25	1/25	3/25	12.0
12	2/18	2/18	2/18	2/18	11.1

TABLE V: PREDICTED EFFECTS OF FACILITIES FOR PREVENTION OF WATER CONTACT

Proposed Facility	Activities Which Would be Eliminated	Duration of Exposure Which Would be Eliminated (in Minutes)	Percent of Total Exposure Which Would be Eliminated
Bridges	Stream crossing	142	9.4
Domestic Water supply	Bathing and clothes washing	537	35.4
Recreational	Playing	773	51.0
All Three	All of above	1,452	95.9

Discussion

It has been postulated that reduction of water contact is as effective as reduction of snail populations in controlling the transmission of bilharzia (5). The question remains however: which types of water contact are most important to reduce? The information presented contributes to the assessment of the relative benefits of preventing various types of contact, and it indicates the most important age group for a program of this type. The first report on water contact in Puerto Rico indicated that the frequency of activities such as clothes washing and bathing were inversely related to the presence of a public water supply (6). The provision of safe water to all homes in Llanos Adentro should eliminate bathing and clothes washing as causes of contact, and thus reduce the exposure of the observed population by 537 minutes out of 1,515, or 34.4% (Tables III and V). However, play activity of children caused the greatest exposure to water. Thus a program to reduce water contact should concentrate on providing protected waterbodies for play activities such as swimming and fishing, thereby eliminating 51% of the exposure (Table V).

Although water contact during stream crossing has been reduced in Venezuela by construction of foot bridges (7), this should have low priority in Llanos Adentro since less than 10% of the total exposure to water occurs due to this activity (Table V).

A comprehensive study on water-contact activities in Egypt indicated that clothes washing resulted in the most water contact of any activity (8) in contrast to the data from Puerto Rico which indicate that play activity was the most important. In the Egyptian study it is surprising that no water contact was observed related to irrigation practices, since this has always been assumed to be the most important type of water contact activity for the Nile area.

Summary

Water contact patterns of people in a bilharzia-endemic watershed of Puerto Rico were studied for six consecutive days in October of 1966. Observers were unobtrusively stationed along a river and at a small pond in Llanos Adentro of Aibonito, noting the occurrence of contact with the water, the type of activity, and the age of the person involved. Children of school age had the most water contact of any age group and play activities accounted for the majority of the water contact observed. It was concluded that a program to control bilharzia by reducing water contact should concentrate on providing recreation for school-age children which does not expose them to water containing schistosome cercariae.

Resumen

Durante el mes de octubre de 1966 se llevó a cabo en el barrio Llanos Adentro de Aibonito un estudio para determinar la relación existente entre la población y las aguas contaminadas con larvas de bilharzia. Se apostaron observadores inadvertidamente a lo largo de un río y un pequeño charco, durante los 6 días de estudio, anotando estos la ocurrencia de los contactos con el agua, el tipo de actividad y la edad de la persona envuelta. Por medio de estas observaciones se pudo determinar que los ni-

ños de edad escolar al enfrascarse en actividades de juego venían en contacto con las aguas con mayor frecuencia que todas las otras edades observadas. Se concluyó que un programa de control de la bilharzia encaminado a la reducción de los contactos humanos con las aguas, deberá de enfatizar la provisión de facilidades recreativas para los escolares de manera que estos no vengan en contacto con las aguas infectadas por las cercarias de los esquistosomas de Manson.

Aknowledgements

The authors are grateful to Mr. Juan Palmer, Mr. Franklin Ortiz, Mr. Luis Vázquez, Mr. Alfonso Quirindongo and their Bilharzia Control crews from the Bureau of Vector Control Puerto Rico Department of Health, for their assistance in this study.

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UNSOLVED PROBLEMS OF HEART TRANSPLANTATION

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On the receipt of information that human heart transplantation had been attempted in December 1967 (1, 2, 3, 4), an element of concern was created as to where we really stood in factual information available concerning the ability to control the immune response or to type human cells with enough accuracy to permit anything beyond a dramatic temporary and short lived survival period as evidenced by the dismal results in animal experimentation up to that point in time.

Because of this radical departure from accepted surgical philosophy and in order to justify the surgical procedure in any way there would, of necessity, be information, new and in contradiction to known scientific fact up to that time, available in published reports.

In order to find a scientific basis for the dramatic news a careful search was undertaken not from the standpoint of the immunologist but rather from that of a cardiac surgeon to determine if the responsibility of actually performing a human heart transplant was justified and, if in reality it was feasible in any way even on a human experimental basis. Only the ideas and reports of experts in the field were used in this report to attempt to gain some insight into the state of our knowledge as expressed in scientific reports at a level comprehendible to a cardiac surgeon.

Billingham (8) who along with Medawar did much of the early fundamental work in opening our understanding of the immune response quoted in 1965 the following:

"Despite the wide publicity it now receives, organ transplantation in man is still very much an experimental procedure from which a relatively few fortunate "guinea pigs" have acquired a new lease on life. Sufficient progress has been made to make us confident that an effective surgical replacement of several vital organs lies close within our grasp, and we are curious to know what the ultimate limits of its application will be. The attainment of this end clearly requires yet more imagination, originality, and sustained efforts at the fundamental level in the laboratory."

Ravdin (9) one of the more respected medical educators of our time brought to our attention the following in respect to the application of the scientific method to the care of patients.

"The application by surgeons of basic

From the Division of Thoracic and Cardiovascular Surgery, University of Alberta Hospital, Edmonton, Alberta, Canada.

Presented to the Puerto Rico Chapter, American College of Surgeons, February 23, 1968.

research to the practical problems presented by patients is frequently in the headlines, while the painstaking efforts of an imaginative scientist who made the fundamental observation is all too frequently overlooked by clinician and layman alike. Applied research is important and valuable, but it is impossible without pure research."

Cellular Individuality as the Primary Cause of Rejection

Since it will soon be apparent that the immune response is a fundamental part of the living process of a cell membrane, and that it stems from the genetically transmitted individuality in all living forms the basic workings of the cell factory must be considered

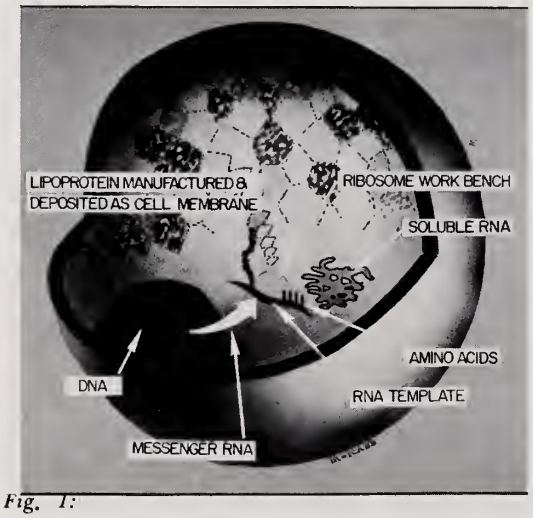


Fig. 1:

The sperm with its individual D.N.A. and the ovum with its equally individual D.N.A. unite to form a new individual. At this time of fertilization a new D.N.A. pattern of genetic code is created. This genetic code (D.N.A.) is responsible for the elaboration of templates of R. N. A. for every cell in the body. This is elaborated through what is termed messenger R.N.A. which passes out from the nucleus to form this template or pattern for the formation of proteins in the cytoplasm of the cell. This template (R.N.A.) determines the amino acid sequences upon which protein specificity depends. The line up of these amino acids occurs on a ribose work bench in the cell which staples the amino acids in their appropriate position to form the new lipoprotein which passes up to form the cell membrane. The pattern of these lipoproteins is determined by the R.N.A. template and this is individual – specific. The only two completely identical cells with the same R.N.A. template would be identical twins.

The spherical wall of the cell is made up of mosaics of many different lipoproteins among which there are many antigenic specificities. The collection of the D.N.A. on the chromosomes of the nucleus of the cells are called loci. There are certain specific areas, several in number, that are specifically responsible for histocompatibility. Genetecists are beginning to unravel the mystery of these loci on the chromosomes and much of the early work was done in mice strains. In the mice the H2 locus was identified as the major area of histocompatibility. These forms were found to have 18-20 alleles for formations of D.N.A. which could be present at a histocompatibility locus. Only one of these alleles could be present in any one locus in any one individual, but it did indicate the permutations and combinations that could occur at each locus and of course there were many of them scattered through different chromosomes in the cell such that matching would present a complex problem

if it were to be complete and of course it never could be. Even though there was fairly good matching at the H2 locus in the chromosome, delayed rejection could occur from incompatibilities at other minor loci in other areas of the same chromosome and of other chromosomes in the nucleus. In mice it was felt there were at least 12 other histocompatibility loci. Dissimilarity at these minor loci produced a progressive rejection of less intense and more delayed nature. Botha (10) stated that the probability of a homograft being compatible would vary according to the closeness of the genetic relationship between donor and recipient. This supports the return to the fundamental concept that the individuality of the cell is relayed from the D.N.A. by means of the messenger R.N.A. to the template R.N.A. which decides the pattern of the proteins of every cell of that individual in the lifetime of the organism.

Transplantation

There are several different types of grafting procedures. The autograft is that situation in which tissue or organ is changed to a different position in the body. In this situation the donor is also the recipient. In animals as far as the heart is concerned this makes a totally denervated heart that is removed from the body and returned to its orthotopic position. The isograft is that situation in which the donor and recipient are genetically identical as in identical twins. Under these circumstances they share the same R. N. A. template and therefore rejection is not a problem. In the allograft the donor and recipient are genetically dissimilar but still in the same species. The histocompatibility centers on the loci on the chromosomes are never identical, however under certain circumstances less incompatibility can occur in certain persons than in others and the closer the genetic relationship the less intense the incompatibility. In the zenograft the donor and recipient are of different species.

If has long been known that tissues can be grafted between genetically identical individuals, however it has also been known for many years that grafting between genetically dissimilar individuals produces what is now known as the *"rejection phenomenon"*.

That this rejection phenomenon is an immune reaction is based on the evidence described by Raffel (11).

1. *Chronology of Rejection*

In Medawar's original work in 1944 (12), he showed that grafted skin usually sloughed in 10 to 14 days after its first applicaton to an homologous recipient. This reaction is known as the *first set rejection.* If tissue from the same donor is reapplied to the same recipient, rejection occurs much more quickly. This accelerated reaction is known as the *second set rejection.* The implication is that the first graft requires time to induce an immunologic response, while the second graft is quickly rejected by an already immunized subject.

2. *Specificity*

The specificity of the graft rejection is another characteristic of an immunologic phenomenon. The second set rejection occurs against the tissue of the donor supplying the first graft. It is therefore *individual-specific.* Conversely a second graft to the same recipient, but from a different donor, will not exhibit this accelerated "se-

cond set" rejection, unless by chance the two donors share antigenic components.

3. *Immunologic Suppressors*

Another support that this is an immune response is indicated in the fact that radiation, steroids, and radio-mimetic drugs, as well as antilymphcytic serum, will affect the donor response to the first set grafts.

4. *Tolerance Induction*

Fetal animals injected with cells of a potential graft donor can be rendered tolerant to transplants in post-natal life. The tolerance induced is unlike immunosuppresive agents in that it is highly individual-specific but unfortunately impractical in man at the present time (13).

5. *Cell Transfer*

As in the case of production of antibodies and delayed hypersensitivity states, the rejection state can be transferred from an immune to a normal recipient by means of lymphocyte transfer. This has only been done in animals but does confirm that the principles that the rejection phenomena are immunological in origin. These principles apply to all transplanted vascularized living tissues, such as skin, heart, bone marrow, etc.

Typical Unmodified Cardiac Allograft Rejection

The unmodified rejection of cardiac allografts is now well described in the reports of Lower (14), Shumway (15), (16), Reemtsma (17), and Chiba (18).

The first clinical signs of rejection are lethargy and tachypnea at 48 hours postoperatively. The mean survival time in untreated animals is 7 days, although a survival until 21 days occasionally occurred and in young puppies in the series by Kantrowitz (7) survival up to 120 days occurred in one isolated instance.

A microscopic picture of cardiac allograft rejection is that of an acute granulomatous pancarditis, somewhat akin to rheumatic fever.

Within three hours of transplantation, the superficial and inner layers of the heart demonstrate infiltration of lymphocytes about the blood vessels. By six hours post-transplant, other cells have joined in the perivascular infiltration. By 24 hours some swelling of the vascular endothelium has occurred and giant cells have appeared. Little more occurs until about the eighth day at which time there is a sudden intensification in the inflammatory reaction, marked endothelial hyperplasia of arterioles, followed shortly by massive cardiac muscle death occurs.

The sensitized lymphocyte of the recipient comes in *intimate contact* with the tissues of the donor organ for allograft rejection to occur. In figure 2 (not included) taken from the work of Porter and associates, in an electron microscopic view the sensitized immunocyte marked L with its capsule in direct contact with the donor cell marked E in a rejecting kidney graft is clearly demonstrated.

Associated with these local effects is often a systemic reaction characterized by fever, anorexia, malaise, elevated white cell count and elevated gamma globulins (20).

Causes of Transplant Failure

Although technical difficulties may occur, which result in bleeding or cardiac failure early after the orthotopic transplant, the main problems encountered are

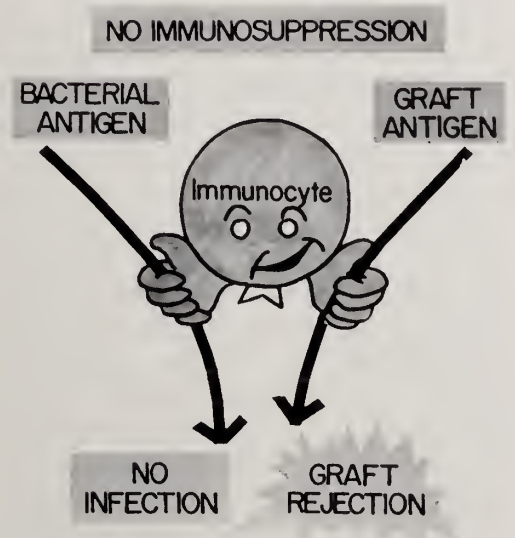


Fig. 3

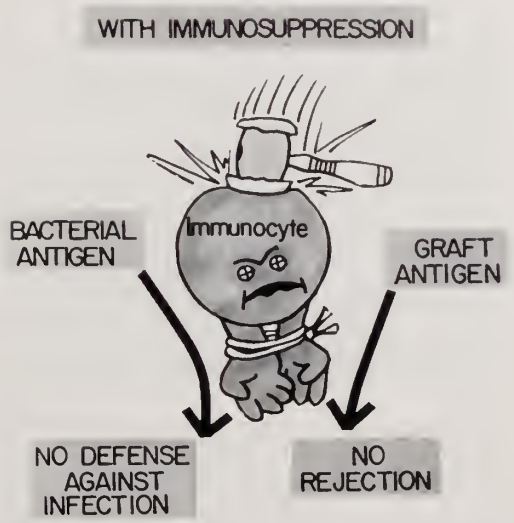


Fig. 4:

those of rejection of the organ by the host, and the complications of immunosuppression.

The exact mechanism of allograft rejection is still not completely clear. According to the current evidence (21), (22, antibodies probably play little role in the "first set" allograft rejection, however controversy still exists in this respect.

The cells of the recipients' reticulo endothelial system, mainly lymphocytes, are sensitized to the lipoprotein constituents (antigen) of the transplaned organ's cell membranes. The contact with the antigen causes the lymphocytes to proliferate extensively. The sensitized lymphocytes then directly attack the donor cells with destruction of their cell membrane. The brunt of both the early (acute) and chronic (late) organ rejection is born by the vasclature of the allograft.

Chronic rejection, in the heart in animals, delayed in its appearance as a result of immunosuppression, is characterized by progressive endothelial proliferation leading to vascular occlusion. This is clearly shown in the work of Lower et al (14).

Immunosuppression

The immunological mechanisms which lead to graft rejection is the same system that permits our survival on this planet. Immunosuppression is an attempt to suppress this fundamental protective mechanism. Let us review briefly the main immunosuppressive systems.

1. Cortisone blocks the uptake of the antigen from the donor cells by the lymphocytes in the host.

2. Radiation, Imuran, (Azathicprine) and Actinomycin D. produce a leukopenia that is the result of inhibition of the mitoses of the nuclei of the reticulo endothelial system. There is also inhibition of D.N.A. and R.N.A. and the production of most proteins. Nucleic acids are also altered and there is actual reticulo endothelial cell destruction, altering all responses to foreign protein including micro-organisms.

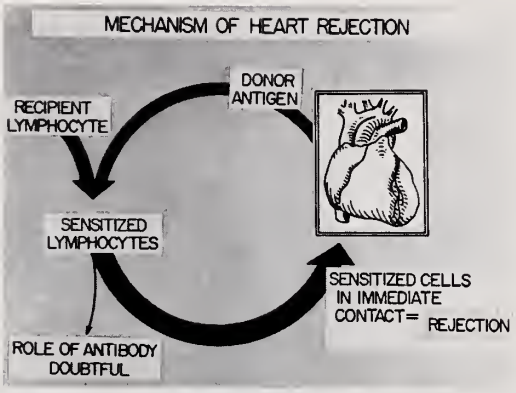


Fig. 5:

Starzl (24) and Abaza (31) have described the use of antilymphocytic serum. This is produced by injecting horses with extracts of liver, thymus spleen and lymph nodes with the production of a serum that will reduce lymphocytic activity and antibody activity. This helps to drop the dose of conventional immunosuppressive drugs but does not prevent rejection.

Complications of Immunosuppresive Therapy

The majority of allograft patients experience repeated episodes of threatened rejection as late as three years after transplantation, and approximately half of the renal transplantation failures are due to rejection.

The intensified immunosuppressive therapy necessary to reverse a rejection crisis represents a threat as serious as rejection itself, leading to increased patient susceptibility to infection by viruses, fungi or bacteria. These infections represent a principal cause of death in clinical transplant patients accounting for virtually all fatalities not caused by graft rejection.

Hill and associates (26) described a syndrome known as transplantation pneumonia characterized by acute pulmonary infection coinciding with acute rejection crises. This syndrome was responsible for 26 of 32 fatalities following renal transplantation. Of these a very large number showed microscopic evidence of cyto-megalic inclusion virus, usually seen only in premature and debilitated infants and not normally causing adult disease. Similarly candida and other fungi (27), normally non-pathogenic in the immunologically competent individual, may cause grave systemic illness in the patient on immunosuppression.

The causes of this increased susceptibility to unusual organisms is related to the mode of action of all immunosuppressive agents.

Lower's results in the animal experiments of heart transplants (14), include complications from drug toxicity such as jaundice, pneumonia and gastro-intestinal bleeding. It is interesting that each of these complications occurred in one or other of the early clinical failures in human heart transplantation.

The available methods of immunosuppression are non-specific in that they affect virtually all the normally protective immune mechanisms, and in many instances are inadequate in that they fail to prevent all rejection phenomena.

Too little therapy and the patient succumbs to his biological abnormality; too much therapy and he is exposed to a constellation of unrelated but equally ominous pathologic processes. The most common single complication is grave systemic infection.

Therefore, even if it is reported that no evidence of rejection is present at the

time of death of a patient with a transplanted heart — but he died of infection — this means only one thing — too much immunosuppression therapy to permit rejection but also too much to permit survival from infection. This is assuming of course that tissue compatibility can not be achieved.

Hamburger (29) studied 67 renal transplants in men and 63 in dogs under immunosuppressive therapy for periods of time from several weeks to 7 years more than 1 year in 32 human transplants. He made observations on those patients which suggest to him that the image of rejection has been over simplified.

Tissue Typing

In cardiac transplants of course any tissue typing must be of a prognosticatory value and not retrospective. There are two main types of tissue typing today. Leucoagglutination of mixed leucocytes as developed by Van Rood and the lymphocytotoxic tests of Terasaki represent the two main forms.

Van Rood (30) has demonstrated 12 leucocyte antigens which he felt belonged to one system.

Terasaki (28) described 6 major lymphocyte groups using 154 antisera. As yet there seems to be no absolute correlation between the findings of Van Rood, Terasaki or Dauset from a prognostic standpoint. As well Dauset (32) recently defined a system HU-1 and he defined 10 main leucocyte groups with 50 antisera.

Starzl (24) recently performed 6 liver transplants, using Terasaki's method of tissue typing.

The results of these patients which had careful histological cellular typing consisted of 2 deaths, one at two months and one at four and a half months. Both of these had mis-match at major systems. Of the four living patients, the one at 7 months had the best matching and was doing well, one at 6 months is in trouble with cirrhosis and had a 5-7 combination mismatch, as did a patient at 3 months who although doing well at that period had an early rejection crisis. One other patient at one week is too early to assess. Thus even under these ideal situations perfect matching is not yet possible. However when this series is compared with a previous series of 7 patients in which no tissue matching was undertaken and in which the longest survival was 23 days, it shows a marked improvement in terms of the length of time of survival.

It has been claimed that the results of kidney transplantation are so good that it is justifiable to perform human heart transplants. When one reviews the fifth report of the Registry of Kidney Transplantation (1967) which includes 1178 cases of which 620 are from unrelated donors the results are far from gratifying. The best results with local radiation to the graft as well as immunosuppressive drugs is that 1 in 3 lived 1 year and a little over 1 in 4 lived 2 years. With cellular matching these statistics have been improved but still have a long way to go to consist of predictable satisfactory results.

In the long term follow-up of human renal transplants and in animal heart allografts stenosing arterial changes seem to be of major importance and are most likely due to repeated rejection crises (Porter) (19).

Summary

Concern has been voiced over the acclaim accorded to a technical procedure in heart transplants without explanation of our state of knowledge of the rejection phenomena.

The rejection phenomena appears so fundamental that should it be possible to prevent it (and this is not the case in an acceptably high percentage) either by tissue typing or controlled suppression - this then would be the breakthrough - not the surgical procedure which uses well understood techniques established a decade ago.

There is no evidence in renal transplantation that the rejection phenomena is avoided; it is merely delayed. The kidney can do its work on 1/10 or its glomeruli. This is probably not so in the heart.

The results of animal heart transplants well done and well documented demonstrate a mean time of survival of 17 days with immunosuppression therapy. Occasionally animals live longer but that in all the long term survivors there is stenosing coronary arteritis of a type similar to that seen in kidney transplants, with or without immunosuppressive therapy.

That the heart, unlike the kidney is an unpaired organ that must do work from its insertion. There is no supportive pump systems as yet available to tide patients through crises of rejection.

Tissue typing can be worked out in renal transplant patients without the need for the more massive surgical experiment of the human cardiac transplant at this point of time.

That a wealth of information has been provided by basic researchers in genetics and immunology but the literature appears to indicate that this is but a beginning of our knowledge. Until tissue typing is more precise, cardiac surgeons would be wise to adopt a conservative approach and return to the experimental laboratory.

That the fundamental confirmation of the animal studies that the heart will do work in the orthotopic position, as predicted in animals, for a short period of time has been accomplished in humans. This merely confirms, along with the complications that occurred in the other clinical cases of heart transplants what was already well documented in animal experimentation.

That the breakthrough, it if comes, will be by careful methodical research at the cell level by scientists trained to do this work.

Aknowledgements

I am indebted to Dr. R. T. Brownlee, Resident in Surgery, Dr. A. Mandel, Research Fellow in Surgery and Dr. S. Singh, Colombo Plan Appointee for their help in scanning the literature; to Dr. G. Bain Department of Pathology for advice and to Ralph McNabb, Medical Illustrator and M. Meeuse, and Mrs. U. Engelhardt of the Department of Photography, University of Alberta Hospital, for preparation of visual aids.

Sumario

Existe preocupación por el recibimiento entusiasta de una técnica quirúrgica para el transplante de corazón, sin dar en cambio ninguna explicación de nuestros conocimientos actuales acerca del rechazo de los órganos transplantados.

El rechazo de órganos es una cuestión tan fundamental que de ser posible el evitarlo (lo que no es cierto en un porcentaje aceptablemente alto) tanto por tipicación

de tejidos o por supresión controlada, constituiría la solución al problema y no la técnica operatoria la cual emplea procedimientos quirúrgicos establecidos hace ya más de una década.

No existe evidencia en el transplante de riñón que el mecanismo de rechazo sea evitado, este es simplemente diferido. El riñón puede realizar su trabajo en una décima parte de sus glomédulos lo que no es igual para el corazón.

Los resultados de transplante del corazón realizados en animales han demostrado que el promedio de supervivencia con terapia inmunosupresiva es de 17 días. Ocasionalmente algunos animales viven más tiempo pero en todos los de supervivencia más prolongada se desarrolla una arteritis estenosante de las coronarias similar a la que se ve en los transplantes de riñón con o sin terapia inmunosupresiva.

El hecho es que el corazón a diferencia del riñón es un órgano impar y deba realizar su trabajo desde el mismo momento de su inserción. No existe en los momentos actuales ningún sistema de bombas de soporte utilizables para ayudar a estos pacientes durante la crisis de rechazo.

La tipificación de tejidos puede realizarse en pacientes de transplante renal sin la necesidad de los mayores experimentos clínicos necesarios en este momento para el transplante del corazón humano.

Un cúmulo de información ha sido suministrado por investigadores básicos en genética e inmunología. Esto parece sin embargo no ser más que el principio de nuestros conocimientos. Hasta tanto la tipificación del tejido sea más precisa, sería prudente que los cirujanos cardiacos adoptaran una actitud más conservadora y regresaran al laboratorio experimental.

La confirmación fundamental en los estudios en animales de que el corazón trabajara en una posición ortotópica, como en los animales ha sido realizada en los humanos por un corto período de tiempo. Esto simplemente confirma conjuntamente con las complicaciones que ocurren en los otros casos clínicos de transplantes cardiacos y que ha sido ya adecuadamente documentada en experimentación con animales.

El que la solución, si esta llega, será la de una investigación cuidadosa y metódica a nivel de la célula por los científicos entrenados en este trabajo.

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Bol. Asoc. Médica de P. Rico
Junio 1968

PHENFORMIN (DBI) IN MEDICAL PRACTICE

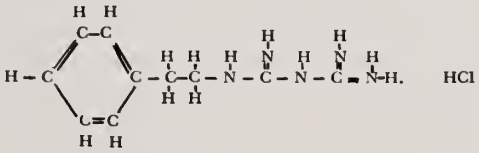
Manuel M Villaverde, MD

The diabetic patient lives not only on diet and insulin, but on a comprehensive plan that may help him to control his dysglycemia. An important part of this plan may be constituted, in a very large number of cases, by hypoglycemic drugs. Among the hypoglycemic agents a physician may select for therapy, phenformin fills a unique role because of its particular actions which beneficially influence not only glucose metabolism but metabolism of fats as well.

Because most diabetic patients improve after taking DBI, particularly the majority in the large group consisting of mature, obese, ketoacidosis-resistant patients, a succint resumé on how to obtain the maximal advantages from the use of this drug will be helpful. "The oral hypoglycemic agent of choice for all types of diabetes is phenformin (DBI) because of its lack of toxicity and ample range of activity (1)." "This drug deserves a range on the priority list of drugs in diabetes therapy (2, 3, 4)."

What Phenformin (DBI) Is

DBI is an oral hypoglycemic agent completely unrelated to the sulfonylureas in both chemical structure and mode of action. Phenformin is N^1-beta-phenethylbiguanide hydrochloride, a white, crystalline, water-soluble substance, that corresponds to the formula:



HCl

The median lethal dose (LD^{50}) is considerably higher than the therapeutic dose, thus permitting an ample therapeutic range of safety. The subacute and chronic toxicity studies showed no ontoward effects of any sort. The law requires that the manufacturer state a pregnancy warning that "adequate data on the fetus with oral agents are not available at the present time, and use in pregnancy can be considered in the experimental stage." Nevertheless, up to the time of writing, no harmful effects on the fetus have been recorded for phenformin (see "Complications of Diabetes").

Side effects produced by phenformin (DBI) were more conspicuous in the past, when no adherence to the slogan "start low, go slow" was practiced. When given in small initial amounts, increasing the dosage by small increments, and particularly when the timed-disintegration capsules are used,

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the side effects are minimal: peculiar taste in the mouth, anorexia, and, more rarely, nausea, vomiting or diarrhea. These symptoms are easily controlled by reduction in dose or withdrawal.

Actions of DBI on Metabolism

It is an accepted fact that phenformin (DBI) does not depend for action on the induction of insulin secretion as do the sulfonylureas. Nevertheless, it cannot regulate glucose metabolism in complete absence of insulin, either natural or injected, and appears to enhance the action of this hormone on cellular glucose uptake by "push-pull" effect. Phenformin "creates" space for glucose within the cell, while insulin "pushes" glucose to pass the cellular membrane (5).

The primary effect of phenformin (DBI) is apparently to increase anaerobic glycolysis (Embden-Meyerhof pathway), which occurs principally in the muscle. Secondary to this effect, cellular glucose uptake takes place and hypoglycemia occurs. Increased anaerobic glycolysis (EM) results in proportionately less glycolysis (hexose-monophosphate shunt) with the consequent production of lesser amounts of triphosphopyridine nucleotide (TPNH), the essential co-factor in the conversion of activated fatty acids to fats, cholesterol synthesis is reduced and subsequently fat mobilization may be increased, thus helping to evoke the convenient weight loss for obese diabetics.

How to Prescribe DBI

DBI is available in 25 mg tablets and 50 mg timed-disintegration capsules. The dosage must be individualized, and for best results it is convenient to start with low doses, with small, gradual increments to adjust to effective levels, and to administer the medication with meals, one or more times a day. If insulin or a sulfonylurea is given, corresponding gradual reduction of insulin or the sulfonylurea should take place for smoother normaglycemic response.

Tablets should be given with breakfast and subsequent meals, one, two, three or four times a day, dosage generally ranging from 50 to 150 mg daily. Some patients respond to 25 mg, while others need 300 mg a day. Dosage over 200 mg are seldom required, which frequently result in symptoms of intolerance.

One capsule is given with breakfast and when a higher dosage is required, a second capsule is given with the evening meal. Additional doses may be given with the first capsule, or with the first and second daily doses (A. M. and P. M.).

In most instances the hypoglycemic response to phenformin (DBI) is apparent within the first week, but in some instances three an four weeks will elapse before the desired response is achieved.

Prediabetes

According to different authors (6, 7, 8, 9, 10,) we may consider DBI to be the drug of choice for prediabetic patients. For years, the concept of prediabetes was more a play in semantics than a consistent part of medical practice (10). This writer belongs to a group, taught by the late Profesor Marañon (12), who for the last thirty years have made efforts to diagnose and treat this stage of diabetes (13, 14). At present there is an almost unanimous agreement that this stage should be treated according to current

practice, and three points are considered of major importance in achieving favorable results: 1) weight reduction, 2) correction of hyperlipidemia, and 3) repose of the pancreas (8, 15). In most cases, a diet low in calories and carbohydrates will achieve these aims. The addition of hypoglycemic drugs will help to obtain a better response from the islets; but insulin and sulfonylureas (insulinogenic drugs) increase the appetite and promote weight gain. In these cases, DBI induces an actual repose of the pancreas, a decrease of blood lipids, and a positive weight reduction.

Stable Diabetes

There is no doubt that the main indication for DBI therapy is the stable adult, ketoacidosis-resistant patient. The drug will not only improve glucose metabolism, but will produce a significant decrease in blood lipids and body weight (16, 17, 18).

Patients presenting this type of diabetes may be of sub-normal or normal weight, though most of them are obese. In most of these cases a reduction of food intake will suffice to control the glucose imbalance; if this does not occur, a hypoglycemic must be added to the treatment. In general terms, when there is a tendency to gain weight, DBI is the drug of choice; when the tendency is to lose weight, insulin or sulfonylureas (Dymelor, Orinase, Tolinase, Diabinese) will be used.

Patients with *subnormal weight* will be better treated with insulin or a sulfonylurea (Diabinese, Orinase, Tolinase, Dymelor), because these drugs will improve the dysglycemia and will help to restore a normal weight. According to Duncan, "a combination of sulfonylurea and phenformin increase the likelihood of success in such patients (15)."

Patients with normal weight will benefit from the use of DBI, insulin or a sulfonylurea (Orinase, Dymelor, Tolinase, Diabinese), or a combination of DBI and a sulfonylurea (15).

Most patients in this group are obese, and close to 90% will respond to DBI with good to excellent control of the disease (19, 20, 21, 22). These patients are better treated with DBI because of its tendency to provoke weight reduction in the great majority of subjects under its effects. Consequently, excepting in those cases which can be controlled by diet alone, DBI is the drug of choice according to a large number of investigators (4, 5, 16, 17, 23, 24, 25, 26). Insulin or insulinogenic sulfonylureas are not as convenient for these patients because these drugs stimulate appetite and the deposition of fat in adipose tissue, that is, the antithesis of the desired weight reduction.

Labile Diabetes

DBI is not suitable for the treatment of labile diabetes when given alone, nor are the sulfonylureas. These patients, children and adults, are insulin-dependent. Ordinarily, the use of insulin is not only imperative, but urgent; still "DBI is a useful adjunct to the conventional modes of therapy in selected cases of unstable diabetes which are insulin? dependent" (27).

There is no doubt that the treatment of a labile diabetic child is extremely difficult, particularly when even small departures from the convenient dose of insulin or the convenient amount of food (carbohydrates, principally) result in notable deviations—the "peaks and valleys" of his glycemia.

DBI "appears to have a place in the overall management of juvenile diabetes, facilitating control without clinical hypoglycemic reactions (28)."

Also, the adult labile diabetic patient is a case that frequently presents "peaks and valleys" of his glycemia following small deviations from his regime. Both the juvenile and the adult diabetic patient will benefit by the addition of DBI to the necessary insulin dosage to obtain a more smooth control, thus avoiding the abrupt changes in blood concentrations that make their treatment so difficult (29).

It is to be noted that in both the adult and the juvenile labile diabetic patient, DBI may normalize the glucose metabolism while a persistent ketosis is present. This is a case of "starvation ketosis," because there is a concomitant reduction of fat synthesis. That is to say, these patients forcibly require insulin for the treatment of this condition (5).

Diabetes With A Concomitant Endocrinopathy

In *acromegaly,* diabetes frequently occurs, its intensity varying from time to time according to variations in pituitary activity. The arrest of activity of the pituitary gland may be followed by a "cure" of diabetes. Polyphagia and weight gain, at least during the early stages and the acme of the disease, are important features of this type of diabetes, thus making it suitable for a DBI regimen.

Diabetes is only slightly more frequent in *hyperthyroidism* than in the general population, though glycosurias are more frequently found among these patients. Both hyperthyroidism and diabetes accentuate the symptons of the other disease; and in the hyperthyroid diabetic patient ketoacidosis and coma develop very rapidly. Treatment will include both conditions. DBI is not indicated in these cases for whom insulin therapy together with a liberal diet is more appropriate.

A large percentage of patients with *Cushing's syndrome or disease* will show impaired glucose metabolism leading to diabetes. In these cases diabetes may be reversible after removal of the adrenal stimulus, or may be permanent. The treatment of the syndrome or disease must be carried out, and diabetes also treated accordingly, with insulin or oral hypoglycemics — particularly DBI when polyphagia and weight gain are manifest symptoms.

Complications Of Diabetes

Ketosis, acidosis and coma are events that may occur due to a more profound metabolic imbalance in diabetes. Ketosis may be treated by diet and drug-adjustment; but both acidosis and coma always require the use of insulin. Any other natural or unnatural occurrence must be considered a complication of diabetes.

Pregnancy is a natural event that complicates diabetes, Symptomatology is more clearly manifest, making the diagnosis of pre or sub-clinical diabetes more apparent. With its progress, insulin requirements increase. A large number of authorities prefer to use insulin during pregnancy, at least when diabetes was known to have existed prior to conception (30). Others do not hesitate to recommend the sulfonylureas and DBI (31). It is interesting to note that DBI helps to keep weight in-

crease within resonable limits. On the other hand, there is also the problem of fetal malformations induced for drugs: both insulin and the sulfonylureas have been incriminated for the production of fetal malformations. A recent review (32) includes sulfonylureas derivatives as inducers of anomalies, but only with a question mark; and phenformin, also with a question mark, as inducer of lactic acidosis. However, it must be noted that even without the use of any drug, the incidence of malformations is high among diabetic offspring (about 80%, according to Dr. P. White) (33). Consequently, the patient may be treated by adjusting her previous schedule to the present condition. During the first months of pregnancy oral hypoglycemics can be given, but following the increased requirements that occur in the latter part, insulin is essential in many instances. DBI is preferred when the patient is obese or has a definite tendency to increased body weight.

Before and during *surgical procedures,* patients must receive enough glucose to prevent ketosis and to maintain nutrition and permit good healing. Most authorities prescribe insulin, even for those patients that can be managed without the hormone. Nonetheless, in recent times there are authorities who do not hesitate to use oral hypoglycemics, in the certitude that these drugs also will help to attain good results. It is preferable to be on the safe side and use insulin in these events.

During *infections,* either acute or chronic, the control of the complicating disease facilitates control of diabetes, and vice-versa. Chronic infections do not require the use of insulin as is imperative in acute cases, but they may be treated according to diabetes itself, that is, using the hypoglycemic that seems to be more convenient in each case.

Different symptons, according to the nerve affected, may announce *diabetic neuritis.* It indicates a poor treatment, and requires adequate reinstatement of diet and medication according to the requirements of the disease (stable, labile, etc.). Attention must be given to vitamin intake, and efforts must be exerted to diagnose and treat other factors involved.

Diabetic cataract is treated as any other type of cataract, the extraction being performed at a suitable time. The treatment of diabetes will be continued as before.

Diabetic retinitis seems to be the consequence of a long-term bad regulation of the dysglycemia. A rigid antidiabetic regimen is the best prophylaxis because retinitis, once established, inexorably progresses toward total blindness. Some patients may improve after hypophysectomy or after irradiation of the posterior segment of the eye. Nilidrin hydrochloride (Arlidin®) may prove beneficial in a few instances.

Transitory *alterations of refraction* are more frequently seen during the periods of metabolic maladjustment or re-adjustment, particularly when insulin is used.

Diarrheic crises may severely impair water and electrolyte metabolism and insulin receptivity. In these cases, insulin must be given together with intravenous glucose. Oral hypoglycemics are not favored in treating severe diarrhea.

Most *skin diseases* complicating diabetes (pruritus, local infections, epidermophytoses, xanthoma diabeticorum), as well as *diseases of the mouth* (gingivitis, pyorrhea)

indicate a poorly regulated dysglycemia and require the establisment of a strong and well-oriented treatment, including hypoglycemic drugs (34).

Finally, and most important, *secondary vasculopathies* (atherosclerosis, arteriosclerosis, high blood pressure, coronary disease, myocardial infarction, diabetic nephropathy of the Kimmestiel-Wilson type, gangrene, and also retinitis, q.v.) are more frequently seen among diabetics than among the general population, thus making it necessary to institute prophylactic measures to check or delay their appearance (35, 36). Adherence to a good plan which includes diet and medication is the best prophylaxis. But we must remember that high blood levels of cholesterol and lipids are indicated as important causative factors of vasculopathies, and that DBI reduces not only hyperglycemia but also the high levels of cholesterol and lipids in the blood (17, 18, 37, 38). For this reason DBI is being recommended as a valuable drug for the prevention of vasculopathies complicating diabetes.

Problems That Arise From The Use Of Insulin

DBI has proven to be extremely useful in the treatment of insulin sensitivity that occurs in many cases of juvenile or adult labile diabetes (see "Labile Diabetes") (39).

It is also very useful in the treatment of insulin resistance, whenever continuously increasing amounts of insulin are needed to maintain the control of hyperglycemia (39). In many instances the addition of DBI will result in the reduction of the required dosage of insulin (40). Seemingly, this resistance is provoked in many cases by the release into the blood stream of insulin antibodies, and the increase in insulin dosage will deteriorate the patient's situation. Insulin will be discontinued whenever possible; in other cases the addition of DBI will help to reduce the dosage, thus improving or controlling the situation. Sulfonylureas may also help, but good results are more constantly obtained with the use of DBI.

Problems That Arise From The Use Of Sulfonylureas

All oral hypoglycemics may present *primary failures,* thus compelling the physician to use a different drug. After a sulfonylurea failure, DBI is the drug of choice; after DBI failure, a sulfonylurea. Sometimes, a combination of sulfonylurea and DBI will solve the situation (41, 42, 43, 44, 45, 46). Otherwise, we have to revert to insulin.

DBI will rarely show *secondary failures* that sulfonylureas so frequently present (41, 43). In the case of a sulfonylurea secondary failure, the problem can be solved by the addition of, or substitution by, DBI for the failing drug. If all fail, insulin will se used instead. In all these cases, when a second drug is added to the ineffective one, it is advisable not to reduce the dosage of the first, and to extend the period of re-adjustment to the final dosage over at least one week.

Other Uses Of DBI

As "by-products" of the use of phenformin (DBI) in diabetes, this drug has been claimed useful in the management of conditions such as hypercholesteremia and

hyperlipidemia, obesity, and, as fibinolytic agent, for the prevention of diabetic degenerative changes.

Hypercholesteremia and hyperlipidemia. It has been reported that phenformin (DBI) can inhibit lipid biosynthesis (47) by making more difficult the conversion of cholestadienol to cholesterol, and can control not only blood sugar but also substantially lowered cholesterol and lipid values (17, 18, 37, 38). We must note that these activities of phenformin are produced only in diabetic patients or those with diabetic-like oriented metabolism.

Obesity. A large number of obese patients may reduce weight under the influence of phenformin (DBI) (25) but this will happen only in subjects that present a metabolic imbalance of the prediabetes type (17, 25). In pure obesity there will be no reduction of weight at all.

Prevention of diabetic degenerative changes. Because of its fibrinolytic activity, phenformin (DBI) might be advised for the prevention of vascular occlusive disease and management of inflammatory disorders, (48) particularly among diabetic patients.

Summary

DBI is N¹-beta-phenethylbiguanide hydrochloride, a hypoglycemic drug with an ample range of safety, that increases anaerobic glycolysis and reduces cholesterol synthesis and body weight in the diabetic patient. It is the drug of choice in prediabetes and non-ketotic, adult, overweight diabetes. It is also advisable in other cases of stable diabetes, and in labile diabetics to help obtain a smoother effect of insulin. Finally, in cases of insulin resistance, sulfonylurea failure, and perhaps some other instances recorded in this paper, the use of phenformin (DBI) may become imperative, or at least advisable.

Sumario

El DBI es el clorhidrato de N¹-beta-fenetilbiguanida, una droga hipoglucemiante que goza de un amplio margen de seguridad y que aumenta la glucólisis anaeróbica a la vez que disminuye la síntesis del colesterol y el peso corporal en los pacientes diabéticos. Es el medicamento de elección para los prediabéticos y los diabéticos adultos con peso excesivo y que no muestran tendencia a la cetosis. También es recomendable para otros casos de diabetes estable y para aquellos diabéticos lábiles que necesitan una ayuda para obtener resultados mas uniformes con el tratamiento insulínico. Finalmente, en los casos de insulinorresistencia, fracasos de las sulfanilureas y tal vez en otros casos señalados en el presente artículo, el empleo de la fenformina (DBI) puede llegar a ser imperativo, o cuando menos, aconsejable.

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36. *Hamwi, G. J., M. Tzagournis and J. F. Seindensticker:* Metabolic Abnormalities in Premature Coronary Disease: Effects of Therapy. Conference on Diabetes Mellitus and Obesity, New York Academy of Sciences, New York, February 27 to March 1, 1967.
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SINDROME DE TESTICULO FEMINIZANTE
Reporte de un Caso

M. Fernández Durán, MD, FACOG

Este sindrome se caracteriza por sujetos con testículos, pero que presentan un fenotipo femenino. Esta condición es mucho más frecuente de lo que se piensa aunque solo hay alrededor de 200 casos probados, reportados en la literatura. McLean Morris (1) hizo una recopilación de unos 80 casos de la literatura hasta 1952, añadiendo cuatro de su experiencia y bautizando este fenómeno de intersexualidad que presenta una combinación de habitus femenino y gonadas masculinas, con el nombre de Sindrome de Testículo Feminizante. Se conoce también como el Sindrome de Morris y Sindrome de Feminización Total (2). Se presenta un caso de observación personal.

Caso

Una joven de 23 años, soltera, de estatura normal y con aspecto somático femenino. Hija única nacida de un embarazo normal. La trajo a consulta una amenorrea primaria. Unicas enfermedades las usuales en la niñez. Facies ligeramente hombrunas pero sin pilificación. No hay desarrollo somático de tipo viril alguno. Mamas excelentes, normalmente desarrolladas. Ausencia de vellos pubianos y axilares. Organos genitales externos normales. Presencia de vagina normal. No había cervix visible ni se palpaba matriz ni anejos. El índice cariopicnótico del frotis vaginal fue 0-83-17. Excreción urinaria de 17— cetosteroides 6.2 mgm / 24 horas. Frotis mucosa bucal negativo para cromatina sexual. P.B.I. 7.5 mcgm %. Gonadotropinas hipofisarias totales 9 HMGU / 24 horas. En la laparatomía se notó la ausencia del útero y las trompas. Del área de origen de los ligamentos infundibulopélvicos se extirparon dos testículos rudimentarios que se conectaban por un cordón de tejido que pasaba por la base de la vejiga urinaria. (Véase fig. 1 y 2) Estas glándulas testiculares estaban constituídas por tejido testicular embrionario, con tejido intersticial poco desarrollado sin evidencia de espermiogénesis, ni de malignidad. Cuatro meses subsiguientes a la operación la paciente no ha presentado trastornos de ninguna naturaleza y hasta ahora no ha necesitado terapia estrogénica.

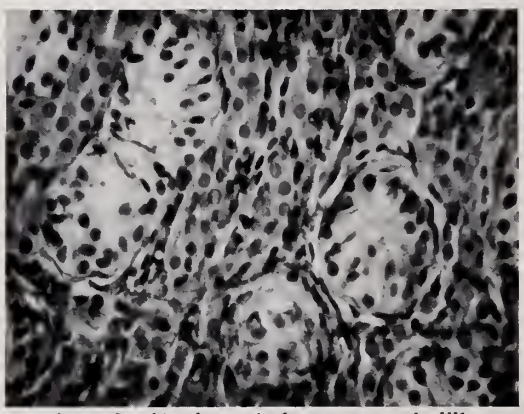


Fig. 1: Sección de testículo muestra tubulillos seminíferos embrionales y células intersticiales (Ley dig) normales. (H&E, X450).

Discusión

Este es un tipo de pseudo-hermafroditismo masculino donde el individuo apaarece externamente como una mujer normalmente desarrollada. El corte del cuer-

po, la distribución de los vellos del cuerpo, la voz y el desarrollo de los senos son todos completamente femeninos. El dato curioso es la falta de crecimiento normal de los vellos pubianos y axilares, característica que le distingue del sindrome de ausencia congénita del útero (5). El útero y las trompas de Falopio están ausentes o están presentes en forma rudimentaria. La vagina casi siempre se encuentra bien desarrollada y usable. La genitalia externa es casi siempre normal aunque a veces puede ser ambigua. Los testículos bilaterales y rudimentarios en este caso se encontraron indescendidos. Cuando descienden se encuentran como el único contenido de hernias inguinales bilaterales.

Los estudios hormonales en éstos sujetos demuestran unas gonadotropinas hipofisarias totales un poco elevadas, o normales como en nuestro caso. Hay una excreción urinaria de estrógenos alta y una de 17-cetosteroides normal para hombres. Los testículos segregan ambas hormonas, el estrógeno responsable de la feminización, y los andrógenos que aunque aparentemente en suficiente concentración, no se manifiestan en los órganos efectores. La teoría más aceptada es que dichos órganos terminales carecen congénitamente de la facultad de responder a la hormona masculina.

El sindrome es de origen genético trasmitido por la línea materna. Afecta a la mitad de los hombres que naturalmente se crían como mujeres (hermanas). Aparentemente se transmite por un factor recesivo, enlazado al sexo. El patrón cromosómico obtenido en los ideogramas de disociación cromosómica es del tipo normal XY.

En estos casos se debe practicar la castración seguida de la administración de estrógenos cuando sea necesario. Estos testículos frecuentemente descienden formando hernias y tienen tendencia a hacerse cancerosos.

Se debe mantener en secreto al sujeto acerca de su verdadero sexo. Quedan como mujeres castradas funcionando adecuadamente y aptas para la vida matrimonial. Usualmente se comportan como en el caso que se reporta, muy femeninas. Estos individuos, así como los hermafroditas, plantean problemas de conducta terapéutica psicológica muy delicados. Estas personas tienen tendencia hacia el sexo al cual creen pertenecer, y el estímulo o urgencia sexual es de la misma magnitud que en la mujer normal — una indicación de que el líbido reside en la psicología femenina más que en las gonadas. Ni los cromosomas sexuales en el núcleo, ni las gonadas definen el sexo. Este se define a la larga por la apariencia que el individuo ha representado ante sus semejantes en cuya convivencia ha desarrollado instintos a tono con el sexo civil establecido. Lo importante es no crear un conflicto entre esos instintos y la sociedad. Autoridades en ésta (3, 4, 5) materia están de acuerdo que impedir el matrimonio, cambiar el sexo civil y lo que es peor aún dar publicidad a estos casos puede llevar a la degeneración sexual y a veces impulsar al suicidio.

Resumen

Una joven de 23 años referida padeciendo de amenorrea esencial. Después de una evaluación médica con énfasis endo-

crinológico, seguido de una laparatomía, reveló los hallazgos del Sindrome de Testículos Feminizante. La histología testicular confirmó el diagnóstico. No se reveló la identidad genética a la paciente. Se acentúa la necesidad de actuar con discreción y juicio en la terapia psicológica de estos casos.

Summary

A 23 years old young "lady" was referred because of primary amenorrhea. After a medical work-up and endocrinologic survey a laparatomy followed. A testicular feminization syndrome was diagnosed. It was confirmed by the histologic examination of the testes. The genetic gender was not revealed to the patient. The psychologic and surgical therapy should be applied judiciously.

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ACTUALIDADES MEDICAS

New Hazards of Chemicals and Drug to Children*

The following chemicals and drugs constitute a serious hazard to children, and pediatricians should warn their patients concerning them:

(1) Fluorocarbon 12

This volatile liquid has been widely used as a refrigerant and aerosal propellant. Since it leaves no toxic residue on evaporation, it recently has been used as a "glass chiller" to produce frosted cocktail glasses. The recent death in Greenwich, Connecticut, of an 11-year-old girl who inhaled fluorocarbon 12 vapor from a balloon, points up the danger that can occur if this usually innocuous substance is mishandled.

Fluorocarbon 12 is a mild intoxicant, but it can kill by suffocation if inhaled in the absence of oxygen, or by cold damage to the larynx if aspirated in liquid form.

All possible publicity as to the potential dangers of inhaling this or any other substance for intoxicative effects is urged.

(2) Pentachlorophenol Sodium

Pentachlorophenol sodium, an antimildew agent, cannot be used safely in hospital linens. Pentachlorophenol poisoning, characterized by fever and profuse sweating (with two fatalities), occurred in St. Louis, Missouri, in infants wearing diapers mistakenly rinsed in a solution of this substance.

The Communicable Disease Center, USPHS, wishes all physicians and hospitals to be aware of the danger of pentachlorophenol sodium. Commercial diaper services should also be notified.

(3) Stramonium "Asthma Powders"

A stramonium-containing powder for the treatment of asthma, which is to be burned (or smoked) and the smoke inhaled by the patient, can become a dangerous substance if misused. A teen-age Connecticut boy was severely poisoned after ingesting two teaspoonfuls of the powder in an attempt to get "high." Physicians should be aware that this and similar substances may be used in psychedelic experiments.

(4) "Big Aspirin"

Claiming prolonged effectiveness (dose-related), several brands of 600 mg. acetylsalicylic acid tablets may soon be marketed again. These are considered to represent twice the poisoning hazard of the familiar 300 mg. tablet. The Subcommittee on Accidental Poisoning would like documented reports of any poisoning (*not* ingestions) by these "doble-size" tablets.

**Statement of subcommittee on accidental poisoning, American Academy of Pediatrics.*

NOTICIAS

Locales

REUNIONES

Junio 7-8 — Convención Semianual — Distrito Este — Hotel Conquistador, Fajardo, P. R.
Julio 4-6 — Convención Semianual — AMPR — Mayaguez.

SECCION DE PSIQUIATRIA, NEUROLOGIA Y NEUROCIRUGIA

La Convención Anual de la Sección de Psiquiatría, Neurología y Neurocirugía de la AMPR se llevará a cabo los días 17, 18 y 19 de octubre de 1968.

Para presentación de trabajos en dicha Convención pueden dirigirse a:

Dr. Gerardo Sanz Ortega
Calle Violeta 1700
Urb. San Francisco
Río Piedras, P. R.

NEW BOOKS

List of books recently acquired by the Library of the University of Puerto Rico, Medical Sciences Campus.

RESPIRATORY SYSTEM:

1. Ciba Foundation,, Symposium on the development of the lung. Boston, Little, Brown & Co., 1967.
2. Engel, Stefan. The prenatal lung. 1st ed. Oxford, New York, Pergamon Press, 1966.
3. Kreyberg, Leiv. Tipos histológicos de tumores pulmonares. Ginebra, Organización Mundial de la Salud, 1967.

GASTROINTESTINAL SYSTEM

1. Brooke, Bryan N. Metabolic derangements in gastro-intestinal surgery. Springfield, Ill., 1967.
2. Cope, Sir Zachary. The early diagnosis of the acute abdomen. 12th ed. London, Oxford University Press, 1963.
3. Chertok, León. Hypnosis. 1st ed. Oxford, New York, Pergamon Press, 1966.
4. Cort, Josef H. Electrolytes, fluid dynamics, and the nervous system. Prague, Pub. House of the Czechoslovak Academy of Sciences; New York, Academic Press, 1965.
5. Denny-Brown, Derek. The cerebral control of movement. Springfield, Ill., Thomas, 1966.
6. Houston Neurological Society. The biology and treatment of intracranial tumors. Springfield, Ill., Thomas, 1962.
7. Institute on New Developments in the Rehabilitation of the Narcotic Addict. Rehabilitating the narcotic addict. Washington, D.C., Vocational Rehabilitation Administration, 1967.
8. Keele, Cyril Arthur. Substances producing pain and itch. Baltimore, Williams and Wilkins Co., 1964.
9. Ranson, Stephen Walter. The anatomy of the nervous system. 10th ed. Philadelphia, Saunders, 1959.
10. Schadé, J.P. The peripheral nervous system. Amsterdam, New York, Elsevier Pub. Co., 1966.
11. Stanley-Jones, Douglas. The kybernetics of natural systems; a study in patterns of control. Oxford, New York, Pergamon Press, 1960.

Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Sept. 26-29, 1968—The Metabolic Basis of Heart Disease, Wayne State University School of Medicine, Detroit, Mich.
Oct. 7-11, 1968—Basic Mechanisms in Internal Medicine, Medical College of Virginia, Richmond, Va.
Oct. 7-11, 1968—Computers In Medicine, University of Wisconsin Medical Center, Madison, Wis.
Oct. 21-25, 1968—Current Concepts of Neurology—Diagnosis and Treatment, University of Maryland School of Medicine, Baltimore, Md.

Oct. 28, 1968—Rheumatic Diseases: Pathology, Immunology, Diagnosis and Treatment, Robert B. Brigham Hospital, Boston, Mass.

OTHER MEETINGS

July 11 — AMA Interspecialty Committee, Chicago, Ill., AMA Headquarters, Board Conference Room, 9:00 a.m. — 5:00 p.m.

July 19-20 — Council on Voluntary Health Agencies, New York, N.Y., Americana Hotel.

July 21 — Council on Environmental and Public Health, Denver, Colo., Denver-Hilton Hotel, all day.

July 22-24 — Air Pollution Medical Research Conference, Denver, Colo., Denver-Hilton Hotel, all day.

Aug. 20-21 — AMA Communications Institute Chicago, Ill., Drake Hotel.

Aug. 25-29 — Council on Foods and Nutrition, San Juan, Puerto Rico.

Aug. 26-29 — Council on Foods and Nutrition Western Hemisphere Nutrition Congress II. Co-Sponsors: American Institute of Nutrition; Latin American Nutrition Society: Nutrition Society of Canada, San Juan, Puerto Rico, Americana Hotel.



Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

ANUNCIOS

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Por motivos de estudio rento o vendo a médico generalista oficina equipada en sitio céntrico (Avenida Roosevelt 1129, Puerto Nuevo, Puerto Rico).

Para más detalles, favor de comunicarse con el Dr. José Rafael Rivera después de las 6:00 p.m. en el teléfono 783-4843. Pueden también solicitarle personalmente en el Departamento de Anestesiología del Centro Médico de Río Piedras.

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1. Cirelli, M. G.: Delaware M. J. *34*:159 (June) 1962.

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COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

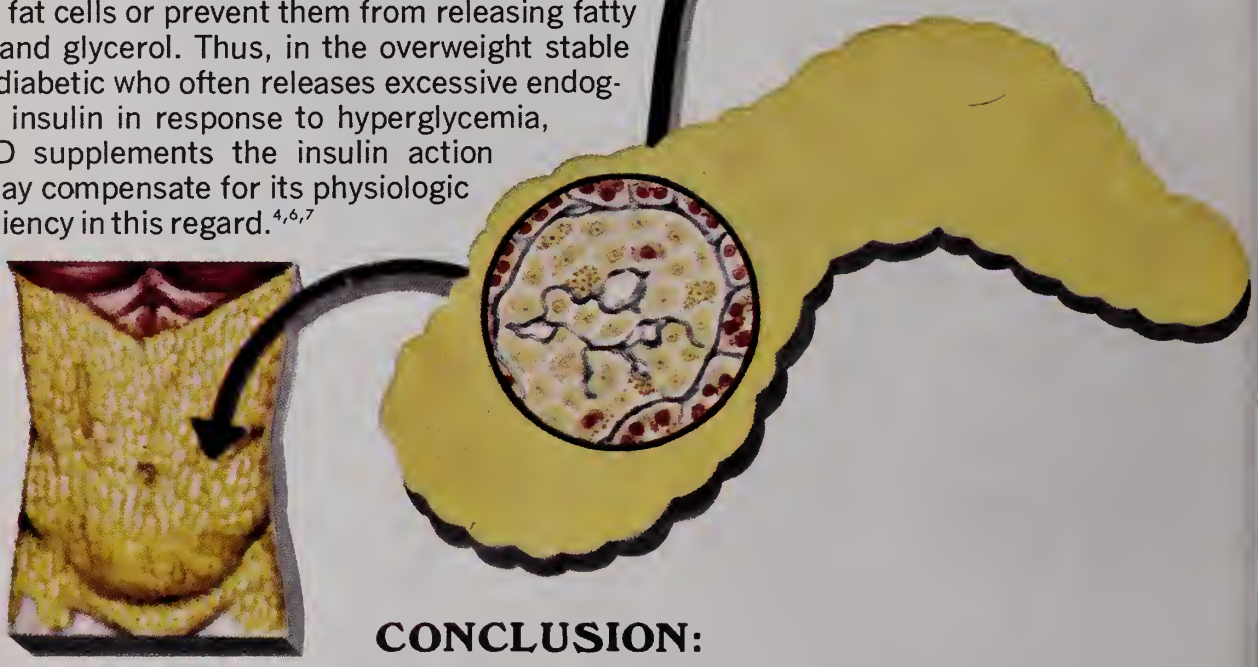
PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

DBI-TD Does Differ From the Sulfonylureas

SULFONYLUREAS stimulate insulin release by the pancreatic beta cells. Endogenous insulin is often present in excess in stable adult diabetics who are overweight.[1,2] This insulin is apparently inefficient in transporting glucose into skeletal muscle, although it retains its activity in adipose tissue.[3,4] Insulin is not only a potent lipogenic hormone, it is also antilipolytic (suppresses fat mobilization from tissues) and thus can contribute to weight gain.

DBI-TD

DBI-TD, on the other hand, acts independently of the pancreas to promote increased glucose utilization in skeletal muscle.[6,7] DBI-TD increases the entry of glucose into muscle cells, possibly by facilitating the action of insulin on muscle; it does not increase glucose uptake by the fat cells or prevent them from releasing fatty acids and glycerol. Thus, in the overweight stable adult diabetic who often releases excessive endogenous insulin in response to hyperglycemia, DBI-TD supplements the insulin action and may compensate for its physiologic inefficiency in this regard.[4,6,7]



CONCLUSION:

DBI-TD acts directly to enhance muscle glucose utilization, whereas sulfonylureas appear to depend upon a supply of insulin releasable from the patient's pancreas for their hypoglycemic effect. Unlike injected insulin or the endogenous insulin released under the stimulus of the sulfonylureas, DBI-TD does not promote the conversion of glucose to fat or prevent the mobilization of fatty acids from the adipose tissue depots of the body.



This is Why DBI-TD should be your Drug of First Choice for Most Stable Adult Diabetics

who are overweight and diet-unresponsive

DBI®-TD

(phenformin HCl)

timed-disintegration capsules 50 mg.

ALONE among oral hypoglycemic agents... provides more benefits for most stable adult diabetics

- Lowers blood sugar
- Increases muscle glucose utilization
- Reduces insulin oversecretion
- Promotes gradual weight loss*

*Although anorexia has been suggested as a possible basis for weight loss, controlled studies do not support this. In nondiabetic subjects who are overweight, comparable doses of DBI-TD do not induce weight loss or lower blood sugar.

Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis acetonuria without hyperglycemia) which must be differentiated rom "insulin lack" ketosis which is accompanied by acidosis, ind treated accordingly. Lactic acidosis has been reported in ıondiabetics and diabetics treated with insulin, with diet, and vith DBI. Question has arisen regarding possible contribution f DBI to lactic acidosis in patients with renal impairment and ızotemia and also those with severe hypotension secondary to nyocardial or bowel infarction. Periodic B.U.N. determination hould be made when DBI is administered in the presence of hronic renal disease. DBI should not be used when there is ignificant azotemia. Any cardiovascular lesion that could result n severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also available:** DBI tablets 25 mg. Consult product brochure.

References: 1. Yalow, R.S. and Berson, S.A.: Diabetes 9:254, 1960. 2. Grodsky, G.M. et al.: Metabolism 12:278, 1963. 3. Gundersen, K. and Antoniades, H.: Proc. Soc. Exp. Biol. Med. 104:411, 1960. 4. Williams, R.H.: Textbook of Endocrinology, Ed. 3, Philadelphia, Saunders, 1962. 5. Gordon, E.S.: Advances Internal Med. 12:66, 1964. 6. Butterfield, W.J.H. and Whichelow, M.J.: Diabetes 11:281, 1962. 7. Searle, G.L. and Cavalieri, R.R.: Presented at 26th Ann. Meet. Amer. Diabetes Ass., Chicago, June 25-26, 1966.

U. S. Vitamin and Pharmaceutical Corporation, New York, New York 10017

when you want to provide the combined benefits of two accepted agents in the treatment of mild to moderate hypertension. (Contraindications: history of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases.)

when you want to prescribe therapy that is generally well tolerated.
(However, adverse reactions may occur. For a complete listing, please refer to the full prescribing information which is summarized below.)

when your patient wants an easy-to-remember and reasonably priced regimen. (One tablet a day usually costs about a dime.)

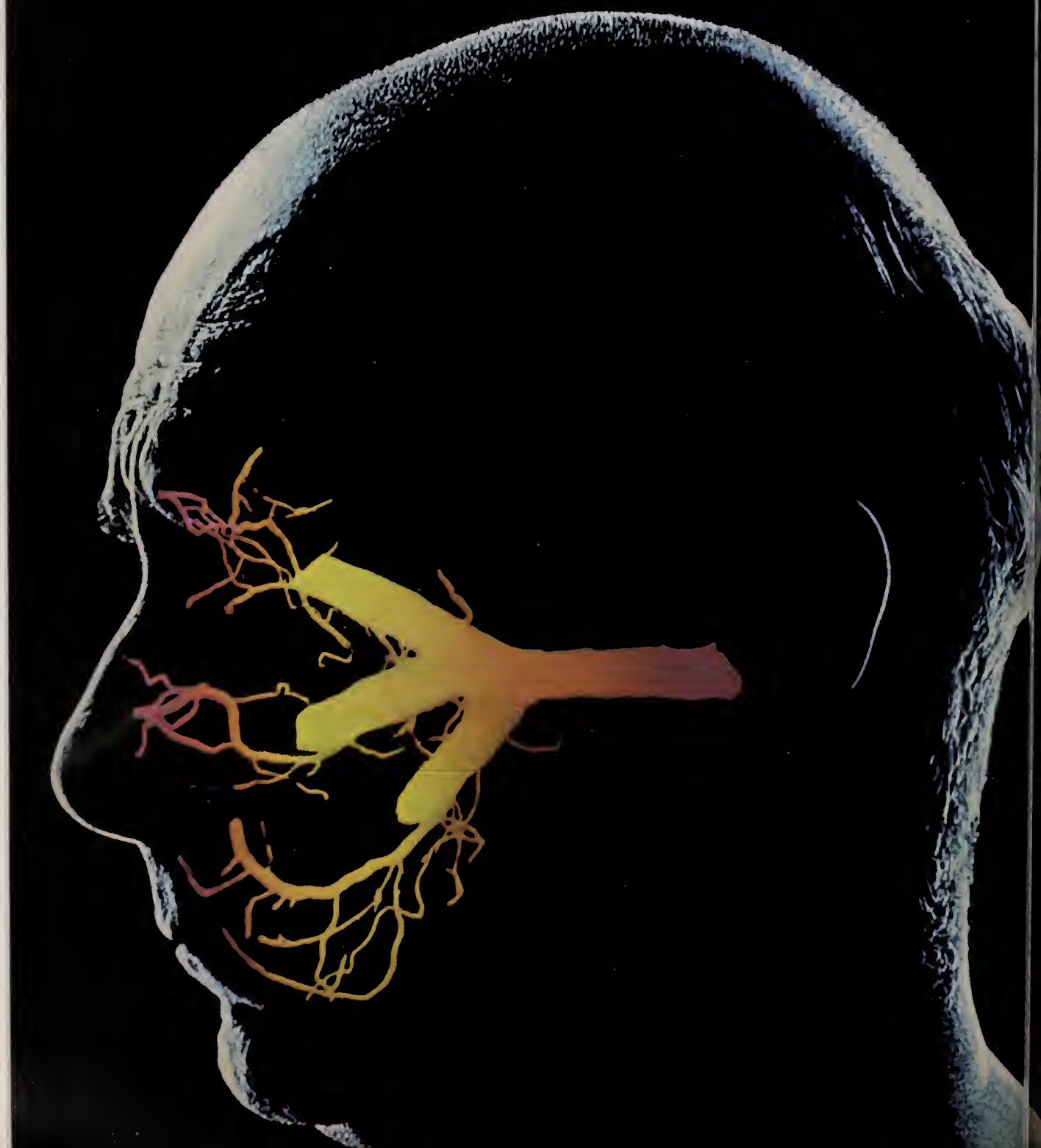
Indications: Hypertension. **Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. **Warning:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue 1 week before electroshock therapy, and if depression or peptic ulcer occurs. **Use in pregnancy:** Regroton should be used in pregnant patients or in women of childbearing potential only when, in the judgment of a physician, its use is deemed essential to the welfare of the patients; adverse reactions (thrombocytopenia, hyperbilirubinemia, altered carbohydrate metabolism, etc.) are potential problems in the newborn. **Precautions:** Antihypertensive therapy with Regroton should always be initiated cautiously in post-sympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue Regroton therapy two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, Regroton should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. **Adverse Reactions:** The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. **Average Dosage:** One tablet daily with breakfast. **Availability:** Pink, single-scored tablets in bottles of 100 and 1000. **For details, see complete Prescribing Information.** (B)46-600-B

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

Regroton® **Geigy**


Grounds...for Regroton®
chlorthalidone 50 mg.
reserpine 0.25 mg.

uncommon relief of uncommon pain



New Tegretol® carbamazepine

Therapeutic breakthrough in non-narcotic control of the pain of trigeminal neuralgia

Warning
Fatal cases of aplastic anemia have been reported following treatment with Tegretol. Agranulocytosis, thrombocytopenia and transitory leukopenia have also been observed.
Complete blood and platelet counts should be done prior to and at regular intervals during treatment with the drug (see recommendations under "Important Note and Precautions") to help in the early detection of serious bone marrow injury. Abnormalities in initial blood tests should rule out use of the drug. Also, patients should be made aware of such early toxic signs of a potential hematologic problem as fever, sore throat, mouth ulcers, easy bruising and petechial or purpuric hemorrhage. Should such signs appear, the patient should be advised to discontinue the drug and to report to the physician immediately.

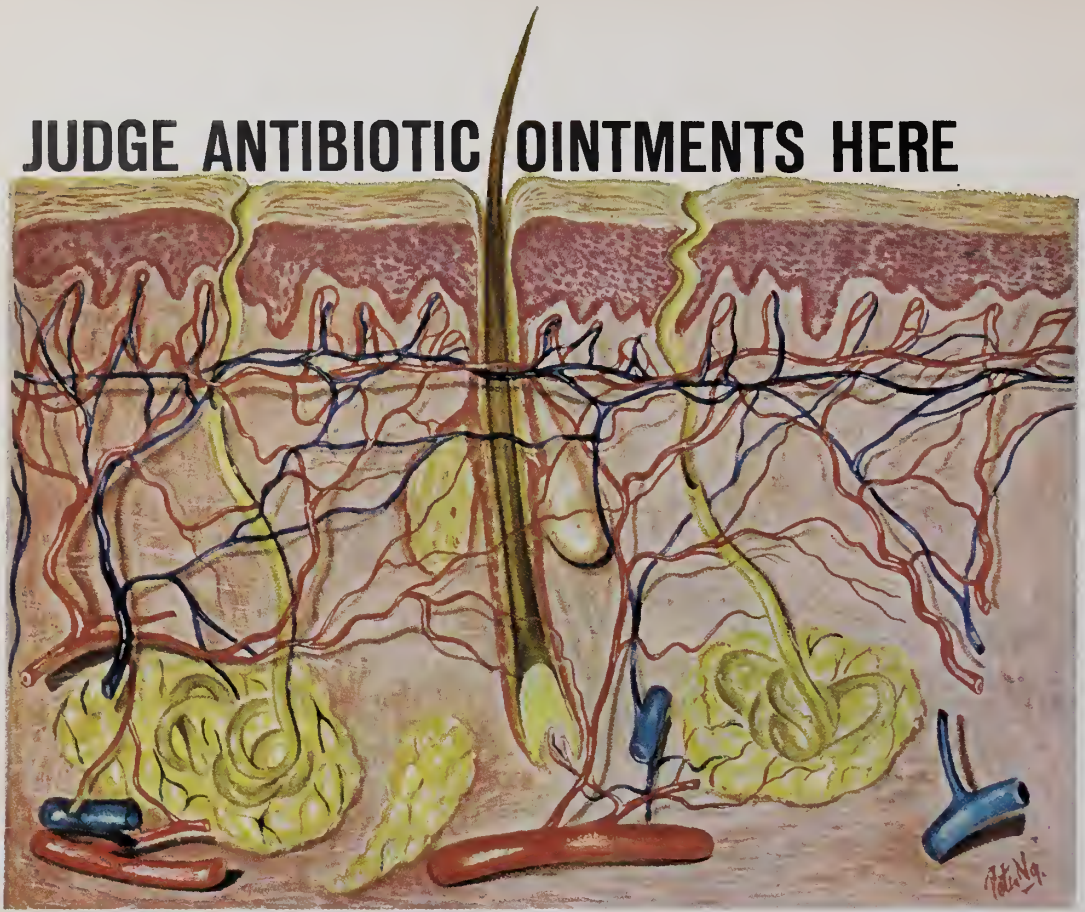
Indication Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. It is not a simple analgesic and should never be administered for relief of trivial facial aches or pains.
Contraindication Do not use in those with a known sensitivity to any tricyclic compound or in those being treated with M.A.O.I. agents. As long a period as possible should elapse before using Tegretol in patients who have been treated with M.A.O.I.'s, with a minimum of 7 days. In such cases, initial dosage should be low and the patient's reaction to gradual increments closely observed.
Important Note and Precautions Familiarity with the clinical symptoms which lead to an accurate diagnosis of true trigeminal neuralgia and with the complete prescribing information, careful patient selection, a thorough examination before treatment and close patient supervision throughout the treatment period are essential to the safe and effective use of this drug.
Where feasible, Tegretol should not be used in conjunction with any potent drug which may increase the possibility of toxic reactions.
In *pregnancy,* the drug should not be prescribed during the first trimester and thereafter only to patients in whom the clinical situation warrants the potential risk. It should not be administered to nursing mothers.
Patients with increased intraocular pressure should be closely observed during treatment with this drug because of its anticholinergic effect.
Because of the drug's relationship to other tricyclic compounds, the possibility of activation of latent psychosis and, in the elderly, of confusion or agitation, should be considered.
Dizziness and drowsiness may occur and patients should be cautioned about the hazards of operating machinery or automobiles and of engaging in other hazardous tasks.
Use cautiously in patients with a history of coronary artery disease, organic heart disease, congestive failure or liver disease.
Before initiating therapy, the following laboratory procedures should be performed:
1. Complete blood and platelet counts which, if abnormal, should rule out the use of the drug.
2. Baseline evaluations of liver function.
During treatment with Tegretol, the following laboratory procedures should be performed:
1. Complete blood and platelet counts should be done at intervals of one week during the first month of drug treatment, every two weeks during the second and third months, and at monthly intervals thereafter for as long as the patient is taking the drug. A trend toward a decreasing white blood cell count should suggest a dosage reduction and more frequent laboratory and clinical evaluations. Should this trend continue, the drug should be discontinued.
2. Liver function tests must be performed at regular intervals during treatment with this drug since liver damage may occur during therapy. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.
3. Periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes.
4. Complete urinalysis and BUN should be done on patients treated with Tegretol because of observed renal dysfunction.

Adverse Reactions Dizziness, drowsiness, unsteadiness on the feet, nausea, vomiting, aplastic anemia, transitory leukopenia, agranulocytosis, eosinophilia, leukocytosis, thrombocytopenia, purpura, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, urinary frequency, acute urinary retention, oliguria with elevated blood pressure, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urine, impotence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency, pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, recurrence of thrombophlebitis, erythema multiforme and nodosum, aggravation of disseminated lupus erythematosus, gastric distress, abdominal pain, diarrhea, constipation, anorexia, dryness of the mouth and pharynx, glossitis, stomatitis, fever, chills, adenopathy, lymphadenopathy, aching joints and muscles, leg cramps, conjunctivitis, left ventricular failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease and congestive heart failure. (Whether these cardiovascular effects are drug-related is not known. However, some of these complications have resulted in fatalities.) The necessity for discontinuing the drug should be dictated by the gravity and severity of the adverse reactions.
Dosage and Administration The drug should always be taken with meals, if possible.
Initial: One-half tablet (100 mg.) b.i.d. on the first day. Thereafter, the dose should be increased in one-half tablet (100 mg.) increments every 12 hours until freedom from pain is achieved. To relieve pain, between 200 mg. and 1200 mg. per 24 hours may be necessary.
Maintenance: Initial control of pain can be maintained in most patients with a dose of 400 mg. to 800 mg. daily. Maintenance doses may range between 200 mg. and 1200 mg. daily.
At least once every 3 months during treatment period attempts should be made to discontinue the drug or to reduce the dose to the minimum effective level.
Availability Round, white, single-scored tablets of 200 mg. in bottles of 100 and 1000. (B)46-820-A
For complete details, please see Prescribing Information.

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Division of Geigy Chemical Corporation
Ardsley, New York 10502

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Results on skin are final proof of any topical antibiotic's effectiveness

No in vitro test can duplicate a clinical situation on living skin. 'Neosporin' (polymyxin B – bacitracin – neomycin) Ointment has consistently proven its effectiveness in thousands of cases of bacterial skin infection. The spectra of the three antibiotics overlap in such a way as to provide bactericidal action against most pathogenic bacteria likely to be found topically. Diffusion of the antibiotics from the special petrolatum base is rapid since they are insoluble in the petrolatum, but readily soluble in tissue fluids. The Ointment is bland and nonirritating.

Caution: As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms and/or fungi. Appropriate measures should be taken if this occurs. Articles in the current medical literature indicate an increase in the prevalence of persons allergic to neomycin. The possibility of such a reaction should be borne in mind.

Contraindications: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components.

Supplied: Tubes of 1 oz., ½ oz. with applicator tip, and ⅛ oz. with ophthalmic tip.

Complete literature available on request from Professional Services Dept. PML.

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brand

POLYMYXIN B-BACITRACIN-NEOMYCIN OINTMENT

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What's all the fuss about bactericidal?

The ultimate aim in antibiotic therapy s o contain the bacterial colony and elimi- ıe infection. Both 'cidal' agents and bac- eostatic DECLOMYCIN achieve this goal.)CLOMYCIN inhibits susceptible pathogens)topping their growth; cidal agents affect the ıogens only while they are growing.

Though the two mechanisms differ, the end eult is the same—containment of the infecting ıanism. *However, a very important attribute ıny antibiotic is its potency against a broad age of pathogens.* DECLOMYCIN not only rs broad-spectrum potency, but high serum tissue levels with persistent activity against e acycline-sensitive organisms. Therapeutic efits continue for 1-2 days after dosage stops elp prevent relapsing infection.

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DEMETHYLCHLORTETRACYCLINE

Lederle

Prescribing information on next page.

For a wide range of everyday infections—respiratory, urinary tract and others—in the young and aged—the acutely or chronically ill.

True broad spectrum

DECLOMYCIN Demethylchlortetracycline should be equally or more effective therapeutically than other tetracyclines when the offending organisms are tetracycline-sensitive.

Contraindication: History of hypersensitivity to demethylchlortetracycline.

Warning—In renal impairment, usual doses may lead to excessive accumulation and liver toxicity. Under such conditions, lower than usual doses are indicated, and, if therapy is prolonged, serum level determinations may be advisable. A photodynamic reaction to natural or artificial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sunburn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photoallergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug at the first evidence of skin discomfort. Necessary subsequent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth — dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; **Tablets:** film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

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Lederle

Open-eyed nights





Too tense to sleep...too tired to get up. Early to bed, late to rise, and not much sleep at that, the patient with severe psychic tension is understandably tired. His tensions and overreactions to the day's stresses may interfere with proper sleep, and his inability to face the day's activities can produce an ever-worsening pattern. By relieving psychic tension, Valium® (diazepam) facilitates sleep, particularly with an h.s. dose. In many patients, the usefulness of Valium has been demonstrated in relieving psychic tension alone or with secondary depressive symptoms. Valium is generally well tolerated and, with proper maintenance dosage, usually does not unduly impair mental acuity or ability.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. Employ usual precautions in the severely depressed or in those [illegible] suicidal tendencies may be present and protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

Adverse Reactions: Side effects most commonly reported: drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50, 100 and 500.

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Valium® (diazepam)

useful for the relief of psychic tension, alone or with associated depressive symptoms

OPY 1

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

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Histaspan keeps protecting against pollinosis...

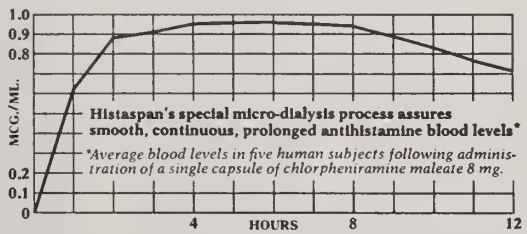
when protection is needed most



Histaspan protects in the early morning. Pollinosis symptoms are often worst in the hours right after sunrise when seed plants discharge their pollens. Taken at bedtime, Histaspan gives allergic patients a good chance for undisturbed sleep and a symptom-free awakening. The reason: Unique among antihistamines, Histaspan provides the proven antiallergic action of chlorpheniramine in micro-dialysis cells for smooth, continuous release of medication through the night and into early morning.

Histaspan protects when there is a sudden rise in pollen concentration. When an allergic patient leaves the relatively pollen-free environment of an air-conditioned home or office to go outdoors, his sudden exposure to higher pollen concentrations may cause particularly severe symptoms. Taken in the morning, Histaspan—with its dependable sustained action—helps provide antihistamine protection at these moments of need, even when they occur late in the afternoon.

Histaspan protects when the patient is most active. Exertion that produces even mild fatigue seems to aggravate pollinosis symptoms. Moreover, functional changes in the G.I. tract during vigorous activity may alter the rate of release of most other antihistamines, resulting in erratic and perhaps inadequate blood levels. Since its release is unaffected by G.I. function, Histaspan maintains therapeutic blood levels even when the patient is most active.



Indications: *For symptomatic relief of allergic manifestations in vasomotor rhinitis, hay fever, urticaria, angioneurotic edema, sensitivity reactions, insect bites, other itching skin conditions including pruritus ani, pruritus vulvae, pruritus of drug rashes, atopic dermatitis and contact dermatitis.* **Contraindication:** *Known hypersensitivity to the drug.* **Precautions:** *Since drowsiness or dizziness may occur, patients should be cautioned about driving or operating machinery.* **Side Effects:** *May include drowsiness, dizziness, dry mouth, disturbed coordination, blurred vision, G.I. disturbance, tachycardia, headache, nervousness, weakness, and urinary disturbances.* **Dosage:** *For both the 8 mg. and 12 mg. strengths: adults and children over age 12, one capsule in the morning, and one at night (q. 12 h.).* **How Supplied:** *Capsules—two strengths: 8 mg. and 12 mg. chlorpheniramine maleate; bottles of 100.*

NEW from USV

HISTASPAN™

brand of chlorpheniramine maleate *in micro-dialysis cells*

USV

USV PHARMACEUTICAL CORP., New York, N.Y. 10017
Producers of DBI®-TD (phenformin HCl)



Tofrānil®, imipramine hydrochloride

Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patient e- ceiving thyroid medication wh this compound was added to t regimen.
Imipramine may block the pha a- cologic activity of guanethidi and other related adrenergic neur blocking agents.
The drug is not recommended t present time in patients under 2 ye of age.
Adverse Reactions: Dryness o he mouth, tachycardia, constipat n, di turbances of accommodation, wea ing, dizziness, weight gain, ur ary frequency or retention, nause nd vomiting, peripheral neuritis, d parkinson-like syndrome, tren rs, rare cases of falling in elderly a- tients, confusional states (wit uch symptoms as hallucinations a dis orientation), activation of psy osis schizophrenics and agitation clu ing hypomanic and manic epi des which may require dosage re ti

Magna cum
epression



For him, commencement.

For his mother, the beginning of his career may seem the end of hers. The end of feeling needed and useful. The beginning, perhaps, of a pathological depression.

Tofrānil can often relieve the symptoms of her depression. If it can relieve her mental anguish, you may be able to help her graduate into a new and fruitful life of her own.

Tofrānil could be her commencement, too.

Tofrānil® Geigy
imipramine
hydrochloride

in depression

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated.

In patients with cardiovascular disease, hyperthyroidism or increased intraocular pressure; in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication or adrenergic neuron-blocking antihypertensive agents; and in those in the first trimester of pregnancy, the precautions discussed in the Prescribing Information should be carefully observed. Although toxic reactions severe enough to require discontinuation of Tofrānil are uncommon, please refer to the Prescribing Information for a description of such instances when discontinuation may be necessary.

or addition of a tranquilizer or
porary discontinuation of the drug,
ptiform seizures, orthostatic
tension and substantial blood
sure fall in hypertensive patients,
ura, transient jaundice, bone mar-
depression including agranulocy-
, sensitization and skin rash
ding photosensitization, eosino-
a, and mild withdrawal symptoms
dden discontinuation after pro-
ed treatment with high doses.
asional hormonal effects (im-
nce, decreased libido, and estro-
c effects) may be observed.
pine-like effects may be more
ounced (e.g. paralytic ileus) in
eptible patients and in those
anticholinergic agents (includ-
ntiparkinsonism drugs).
atient Adult Dosage: Initially,
g. daily, increased, if necessary,
0 or 200 mg. Maintenance dosage
be lower, 50 to 150 mg. daily, if
ible.

Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)R-46-850-C

For complete details, please refer to the full Prescribing Information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

Open-eyed nights





Too tense to sleep...too tired to get up. Early to bed, late to rise, and not much sleep at that, the patient with severe psychic tension is understandably tired. His tensions and overreactions to the day's stresses may interfere with proper sleep, and his inability to face the day's activities can produce an ever-worsening pattern. By relieving psychic tension, Valium® (diazepam) facilitates sleep, particularly with an h.s. dose. In many patients, the usefulness of Valium has been demonstrated in relieving psychic tension alone or with secondary depressive symptoms. Valium is generally well tolerated and, with proper maintenance dosage, usually does not unduly impair mental acuity or ability.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders; athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindications: Known hypersensitivity to drug; children under 6 months of age; acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in treatment of psychotic patients, and should not be employed in lieu of appropriate treatment. As with most CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increase in dosage of standard anticonvulsant medication; abrupt withdrawal in such cases may also be associated with temporary increase in frequency and/or severity of seizures. Advise patients against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance. Keep addiction-prone individuals (such as drug addicts or alcoholics) under careful surveillance because of their predisposition to habituation and dependence. Use of any drug in pregnancy, lactation or in women of childbearing age requires that potential benefit be weighed against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam), such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants. protective measures necessary. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation (initially 2 to 2½ mg once or twice daily, increasing gradually as needed or tolerated).

Adverse Reactions: Side effects most commonly reported: drowsiness, fatigue and ataxia. Infrequently encountered: confusion, constipation, depression, diplopia, dysarthria, headache, hypotension, incontinence, jaundice, changes in libido, nausea, changes in salivation, skin rash, slurred speech, tremor, urinary retention, vertigo and blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should these occur, use of the drug should be discontinued. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are advisable during long-term therapy. Minor changes in EEG patterns (low-voltage fast activity) observed during and after therapy and are of no known significance.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg; bottles of 50, 100 and 500.

ROCHE

Roche® LABORATORIES

Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Valium®(diazepam)

useful for the relief of psychic tension,



new
Lasix®
furosemide
Injection
for I.M.
and I.V. use

in an age
of discovery...
step beyond
the mercurials

when immediate diuresis is desired in cardiac, acute pulmonary, hepatic, and renal edema, and when oral medication is not practical...

prompt, encouraging response

Diuresis with Lasix (furosemide) Injection begins within 5 minutes after I.V. administration (somewhat later after I.M. injection) and peaks in the first half hour. Rapid onset means quickly perceptible relief for most patients (may even be lifesaving in acute pulmonary edema).

short span of action

Diuresis with Lasix Injection is complete in approximately 2 hours, permitting early evaluation of therapeutic response and the administration of a second dose as needed.

generally assured efficacy from onset of therapy

Because of its action throughout the nephron (in Henle's loop as well as in the proximal and distal tubules), Lasix Injection provides enhanced diuretic efficacy equal to or surpassing that of mercurial diuretics. Lasix is often effective in patients who have not responded to other diuretic agents. In medical emergencies, such as acute pulmonary edema, the immediate and intensive diuresis after Lasix Injection may be lifesaving.

dose-regulated response

Diuretic response to Lasix Injection is proportional to the dose administered. When needed, a wide reserve of measurable diuretic efficacy is available by increasing the dose.

convenient dosage form

Lasix Injection is supplied as a sterile solution in ready-to-use, 2 cc. ampules for both I.V. and I.M. administration. No reconstitution required, no large volume to inject.

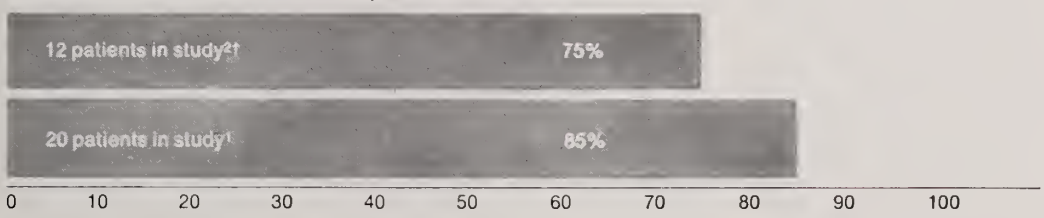
Please see prescribing information which follows...

new Lasix® furosemide Injection for I.M. and I.V. use

in acute pulmonary edema[1,2]...

In a study of 20 hospitalized patients with acute pulmonary edema, Weinstein and Solis-Gil[1] found that "...a 40-mg. dose [of Lasix Injection] consistently produced a rapid diuresis with coincident rapid clinical improvement....most cases responded with an immediate diuresis usually within the first hour....Despite the large quantities of urine voided, there were no apparent ill effects from furosemide administration."[1] (Some patients demonstrated a transient rise in blood urea nitrogen.) The authors concluded: "Results of this study suggest that the use of furosemide intravenously in proper dosage, followed by booster injections...as necessary, is a most effective procedure in the treatment of acute pulmonary edema."[1]

Percentage of patients with acute pulmonary edema who responded satisfactorily to parenteral Lasix: results from two representative studies [1,2]



†All 12 patients in this study had become refractory to thiazides and organomercurials.

in congestive heart failure[2-4]...

efficacy beyond the capacity of mercurials

Davidov and co-workers[2] administered Lasix Injection intravenously to 41 patients with severe congestive heart failure, all of whom had become refractory to thiazides and mercurials: "Although maximum doses of thiazides and organomercurials had been employed until the day of furosemide administration, a further increase in diuresis occurred in each of the patients following furosemide administration. Not only was complete clearing of edema accomplished in all the patients, but even more striking was the roentgenographic demonstration of disappearance of congestion in nine of 12 patients with pulmonary edema by the fifth day of treatment."[2]

in an age of discovery...discover this important agent for the control of edema

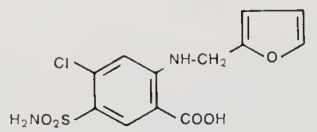
Lasix®

brand of furosemide
Tablets and Injection

WARNING—Lasix (furosemide) is a new, potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Theretore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Lasix (furosemide) is a new diuretic, chemically distinct from the organomercurials, thiazides, and other heterocyclic compounds. It is characterized by: a high degree of efficacy; a rapid onset of action; a comparatively short duration of action; a ratio of minimum to maximum effective dose higher than 1:10; the fact that it acts not only at the proximal and distal tubules, but also at the ascending limb of Henle's loop.

Chemistry—Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The structural formula is as follows:



Pharmacology—Investigations into the mode of action of Lasix (furosemide) have utilized the most recent methods in nephrology: micro-puncture studies in rats, stop-flow experiments in dogs, and various clearance studies in both humans and experimental animals. It has been demonstrated that Lasix (furosemide) inhibits primarily the reabsorption of sodium not only in the proximal and distal tubules, but also in the loop of Henle. The high degree of efficacy is largely due to this unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase and aldosterone. The onset of diuresis following oral administration is within one hour, the peak effect occurs within the first or second hour, and the duration of diuretic effect is 6 to 8 hours. The diuresis following an intravenous injection commences within five minutes (somewhat later after intramuscular injection), reaches its peak within the first half hour and lasts for two hours. Because Lasix (furosemide) inhibits the reabsorption of a very high percentage of the filtered sodium, it is often effective in patients with markedly reduced glomerular filtration rates, in whom other diuretics usually fail. Lasix (furosemide) has been used concurrently with aldosterone antagonists to good advantage. Lasix (furosemide) appears to have a blood pressure lowering effect similar to that of the thiazides.

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix (furosemide) is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired. If the gastrointestinal absorption is impaired or oral medication is not practicable for any reason, Lasix (furosemide) is indicated by the intramuscular or intravenous route. The intravenous administration of Lasix (furosemide) is indicated when a rapid onset of the diuresis is desired, e.g., acute pulmonary edema. **Parenteral administration should be reserved for patients where oral medication of Lasix (furosemide) is not practical.** Until further clinical experience is accumulated, Lasix (furosemide) is not recommended for use in hypertension.

Contraindications—Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound. Until further experience in children is accumulated, therapy with Lasix (furosemide) should be avoided.

Supplementary Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids. Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn. **In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital.** Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. As with any new drug, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions. In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical. There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred. Based on a large survey of physicians and hospitals, both American and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs. Lasix (furosemide) is not available in a combined product with any form of potassium.

Usage in Pregnancy—The use of any drug in pregnancy, lactation, or in the child-bearing age group requires that the potential benefits of the drug be weighed against possible hazards to the mother and child. Reproduction studies with Lasix (furosemide) in mice, rabbits, and rats have produced no evidence of toxicity specific to the fetus. However, Lasix (furosemide) has had only limited use in pregnant patients.

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix (furosemide) is administered, since Lasix (furosemide) potentiates the hypotensive effect of antihypertensive medications. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Although no pronounced effect on carbohydrate metabolism has been demonstrated, periodic checks on urine and blood glucose should be made in diabetic patients receiving Lasix (furosemide). Occasional increases in blood glucose have occurred during therapy with Lasix (furosemide). Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue oral Lasix (furosemide) for one week and parenteral Lasix (furosemide) two days prior to any elective surgery.

Adverse Reactions—Infrequent skin rash, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea may occur. Thrombocytopenic purpura has been reported. There have been a few instances of leukopenia and one report of acute pancreatitis although relationship to the drug has not been established. Lasix (furosemide) induced diuresis has occasionally been accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, flushing, and urinary frequency. Transient pain after intramuscular injection has been reported at the injection site.

Dosage and Administration

Oral Administration: The usual dose of Lasix (furosemide) is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily, e.g., at 8:00 a.m. and 2:00 p.m. Based on completed studies, a maximum daily oral dose of 200 mg. should not be exceeded. Higher doses are currently under investigation. The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

Parenteral Administration: The usual dose of Lasix (furosemide) is 1 to 2 ampules (20 to 40 mg.) given as a single dose, injected intramuscularly or intravenously. The intravenous injection should be given slowly (1 to 2 minutes). Ordinarily, a prompt diuresis ensues. Depending on the patient's response a second dose can be administered two hours after the first dose or later. If the diuretic response with a single dose of 1 to 2 ampules (20 to 40 mg.) is not satisfactory, e.g., in a patient refractory to maximal doses of thiazides, the following schedule should be used under careful medical supervision: Increase this dose by increments of 1 ampule (20 mg.) not sooner than two hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. Parenteral administration should be reserved for patients where oral medication is not practical. The parenteral therapy with Lasix (furosemide) can be replaced by treatment with Lasix (furosemide) tablets as soon as this is practical for continued mobilization of edema. **Treatment of Acute Pulmonary Edema**—Since the diuresis evoked by Lasix (furosemide) given intravenously commences within five minutes and leads to an intensive diuresis, the treatment of patients with acute pulmonary edema with Lasix (furosemide) intravenously has proven particularly valuable. The following dosage schedule is recommended: 2 ampules (40 mg.) of Lasix (furosemide) are to be slowly injected intravenously immediately. This dose should be followed by another 2 ampules (40 mg.) one to one and one-half hours later, if that is indicated by the patient's condition. If deemed necessary, additional therapy, e.g., digitalis, oxygen, can be administered concomitantly. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

How Supplied—Lasix Tablets are supplied as white, monogrammed, scored tablets of 40 mg. in amber bottles of 100 (FSN 6505-062-3336). **Lasix Injection** is supplied as a sterile solution in 2 cc. amber ampules each containing 20 mg.

References: (1) Weinstein, H., and Solis-Gil, V.: The treatment of acute pulmonary edema with furosemide, Curr. Therap. Res. *8*:435, 1966. (2) Davidov, M.; Kakaviatos, N., and Finnerty, F. A., Jr.: Intravenous administration of furosemide in heart failure, J.A.M.A. *200*:824, 1967. (3) Wertheimer, L.; Almondhiry, H., and Khero, B.: Furosemide, a new diuretic in edematous states, Arch. Int. Med. *119*:189, 1967. (4) Dvorak, A.; Grinnell, E. H.; George, R. P., and Sullivan, J. F.: Parenteral use of furosemide for diuresis, Nebraska M. J. *52*:367, 1967.

17268

HOECHST
PHARMACEUTICAL CO.
Cincinnati, Ohio 45229

Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

UNA PINTA DE SANGRE NO PROPORCIONA MAS HIERRO

QUE UNA AMPULA DE 5 cc. DE



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

LAKESIDE

PRODUCTOS PARA PACIENTES QUE UD. VE A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

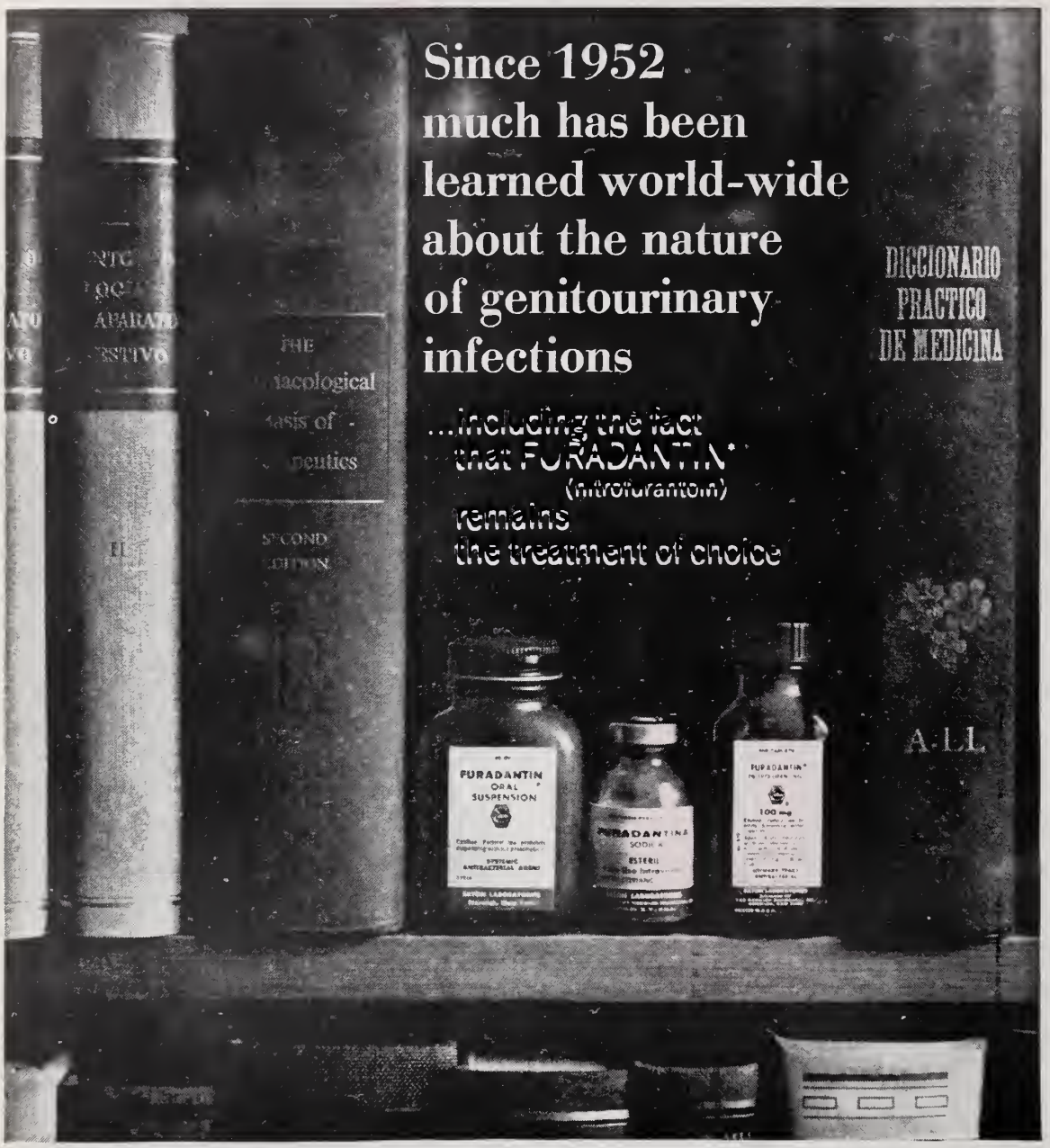
ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.



when urinary infection is suspected, try **Furadantin** first

specific · safe · superior

Furadantin is supplied as Tablets, 50 mg. and 100 mg., bottles of 25, 100, 500 and 1000; and as Oral Suspension, bottles of 60 cc.

EATON LABORATORIES
Division of The Norwich Pharmacal Co., Norwich, New York, U.S.A.

Eaton*

*REGISTERED TRADEMARK

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

Organo Oficial

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Anuncios y Suscripciones:
El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

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HIATAL HERNIA: THE CRUX OF THE MATTER

Laszlo Ehrlich, MD, FACP, FACR

Hiatal hernia (HH), formerly a relatively obscure condition, has become a frequently diagnosed and controversial one, judging from the large number of articles on this subject in medical literature in the past 15 years. It has become of increasing interest to the anatomist, the pathologist, the gastroenterologist, the radiologist, and above all to the surgeons. The X-ray diagnosis of HH has evolved from the simple demonstration of a "pouch-like" structure above the diaphragmatic hiatus, to very sophisticated techniques based on image intensifier, cineradiography, manometry and pH determination. I will present my experience based on the use of simple, old-fashioned X-ray equipment and offer you my conclusions concerning HH.

The first series of 30 cases of HH was published by Akerlund of Sweden in 1926. He classified HH (Fig. 1) into 3 types: type 1: short esophagus; type 2: paraesophageal hernia; type 3: gastroesophageal hernia. This classification is accepted even today in its basic concept, although it was modified by Harrington of Mayo Clinic (16), Allison of England (1), Monges of France (6), Hagarty of Australia (15) and by others. A diagram of the modern classification of HH is shown in Fig. 2.

From the X-Ray Service, San Juan Veterans Administration Hospital.

Presented at the Annual Meeting of the Asociación Médica de Puerto Rico, November 18, 1967.

In 1944, Templeton (33) of USA described in great detail the peculiar behavior of the distal portion of the esophagus which acts as a sphincter at the cardia, although no anatomical proof of a sphincter was demonstrable. He discussed the possible importance of the "pinch–cock" action of the diaphragmatic hiatus and of the restraining effect of the phreno-esophageal ligament. He also revived the special phenomenon of the *phrenic ampulla* just above the hiatus and warned us that this structure may imitate a small hernia (Fig. 3). The importance of Templeton's work on the subject lies in the fact that he foresaw the trouble with these small hernias. In the 40's, however, it was fairly quiet on the hiatus hernia front. The typical clinical picture of HH (heartburns, epigastric pain, etc.) was frequently attributed to peptic ulcer or to the so-called "dyspepsia"; the atypical symptoms of HH (retrosternal pain), to angina pectoris. We roentgenologists, simply wondered how often our large and pretty hernias so impressive in the films did not seem to bother the patients.

The subject of HH became really important in 1950 when Lerche of USA (38) published his new findings concerning the anatomy of the distal esophagus. He introduced two new landmarks (Fig. 4): 1. The *vestibule*, extending from the cardia for 2-4 cm upwards and 2: *The inferior esophageal sphincter* immediately above the vestibule. The same year (1950), Barrett (22), an English surgeon

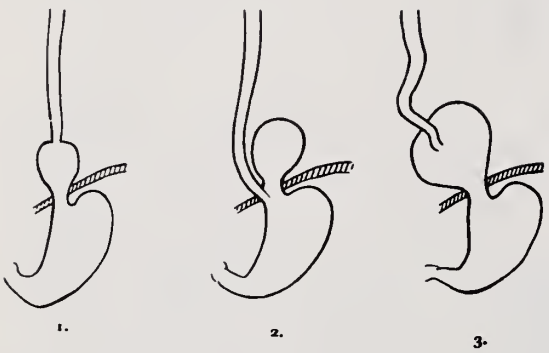


Fig. 1: The original classification of HH into 3 types by Akerlund: Type 1: Short esophagus (congenital or acquired). Type 2: Paraesophageal hernia. Type 3: Gastroesophageal hernia.

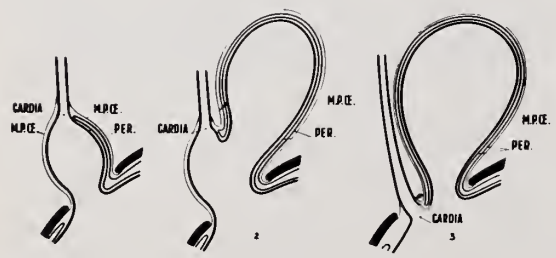


Fig. 2: Diagram of the modern classification of HH. This sketch is of practical value as it shows the most common types of HH: (1) the sliding type; (2) the less frequent type: the sliding hernia with a paraesophageal component; (3) the rare type: paraesophageal hernia, showing the distinct separate passage of the hernia. MPOE: Phrenoesophageal membrane. PER: Peritoneum.

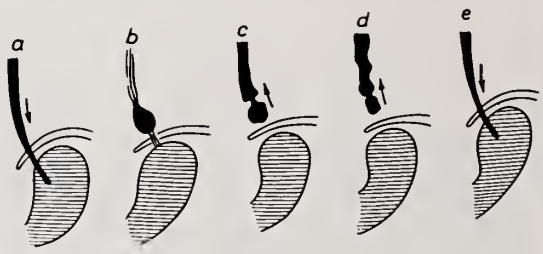


Fig. 3: a. Swallowing thin barium with shallow breathing: The normal tubular aspect of esophagus. b. Deep inspiration: phrenic ampulla appears. c. & d. Sustained inspiration: antiperistalsis chasing the barium cephalad. e. Normal breathing: same appearance as in "a".

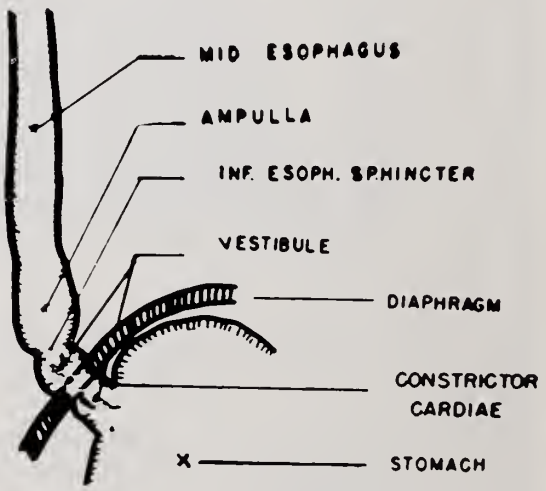


Fig. 4: Diagrammatic drawing, lower two-thirds of the esophagus (Lerche, 1950).

brought into the open the disagreement among all concerned regarding the gastroesophageal junction. He also emphasized the importance of *reflux* and pleaded that the term *reflux esophagitis* be recognized as an entity.

At that time the incidence of HH by Roentgen examination of the upper G. I. tract was about 3 percent. This figure became 50 percent in a paper by Stein and Finkelstein in 1960. This high incidence was attributed by them to careful technique and a broader definition of the term HH (32). Wolf, of New York, introducing a special technique of his own (41), brought the incidence to 63 percent (42). The controversy as to the technique was centered on the demonstration of the small HH. The fact that a paper by Johnson of India described 18 radiological signs for the diagnosis of HH in 1958 (20), and Wolf published an editorial in 1960 entitled *"Definition of the HH"* (39) should be fairly convincing evidence that the matter is not settled. According to his definition, the diagnosis of HH must be based on dislocation of the esophagogastric mucosal junction.

Manometric studies carried out on both sides of the ocean gave a great impetus to the solution of the problem. This method confirmed that the distal 2-4 cm of the esophagus actually behaves as a *physiologic sphincter*, corresponding to the very segment that was described and called *vestibule* by Lerche in 1950. This special segment was designated *a high pressure zone.* Manometry could graphically demonstrate that in case of HH there is upward dislocation of the gastroesophageal junction. The determination of the pH *above* the high pressure zone, shows there is acid reflux. By this time, the fact that the symptoms and the complications of HH are due to the acid reflux was universally accepted. In addition to the esophageal symptoms due to reflux, lately important pulmonary complications have been described in over 50 percent of cases of HH by Urschel and Paulson (36).

For some odd reason, however, most radiologists concentrated on the demonstration of the HH and not on the demonstration of reflux. As far as I am concerned, I began to look for reflux only in the past 4 years. I felt that since the diagnosis of esophagitis is in the domain of the endoscopists, the demonstration of reflux also belonged to him. I suppose the surgeons felt the same way, since I have never received an X-ray request for the demonstration of reflux. At this point I wish to mention that I have found at San Juan Veterans Hospital only 4 cases of surgical repairs of HH up to 1962. Since then, we have had 20 HH operations. Studying this material and the medical literature on the subject, I came to the following conclusions:

1. The X-ray demonstration of *reflux is of primary importance* for patients with symptoms suggestive of HH.
2. The X-ray demonstration of the HH *is of secondary importance.*

These statements, however, should not be construed that we could dispense with the careful technique necessary for the demonstration of HH. This technique and that of the reflux are described in conjunction with the presentation of cases.

Case Reports

Case 1:

This patient had a confusing clinical history. He complained of aphagia rather than dysphagia; he insisted that he had no heartburn. Fig. 5 shows the obvious HH while he drinks a thin mixture of barium continuously. The HH is also demonstrated in the polygraphic study performed with a thick mixture of barium, films being taken both in inspiration and expiration (Fig. 6). No reflux was observed during fluoroscopy. The patient was esophagoscoped 3 days later, and definite esophagitis and reflux were found. Learning this, we repeated our examination on the next day and obtained the most generous reflux (Fig. 7). This time we took films also in the erect position which suggested that the HH was fixed and the His' angle was increased (Fig. 8).

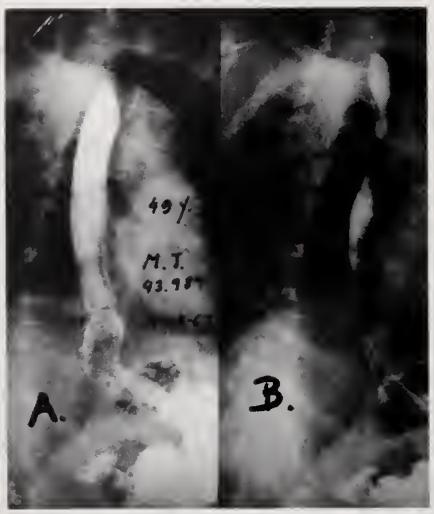


Fig. 5: Case 1. The film is taken while the patient drinks thin barium continuously in the *prone* position with his left shoulder raised. A: shows the width of the hiatus and in this case also the hernia. B: shows the mucosal pattern of the entire esophagus. This is our modification of Wolf's technique (41).

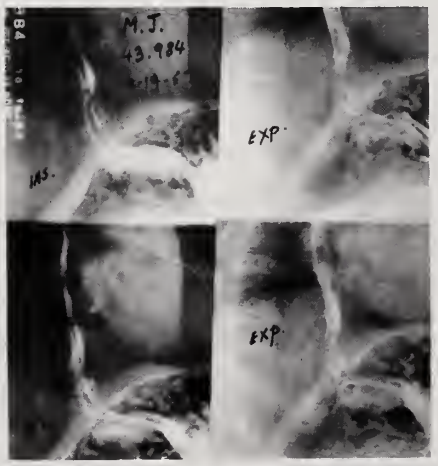


Fig. 6: Case 1. Polygraphic study consisting of 4 views (2 in inspiration and 2 in expiration) taken in rapid succession using thick barium. The position is the same as in fig. 5. The HH is best seen in *inspiration.* We routinely take 2 sets of polygrams: 8 views. This is a modification of Stein and Finkelstein's technique (32).



Fig. 7: Case 1. Documentary evidence of free reflux with spot films. The patient is in the *supine* position, his left shoulder raised; he is instructed to swallow his saliva and to take a deep breath. If he has free reflux, the barium will erupt in a massive fashion into the esophagus up to the aortic arch; since the reflux usually keeps on, there is ample time to take spot films.

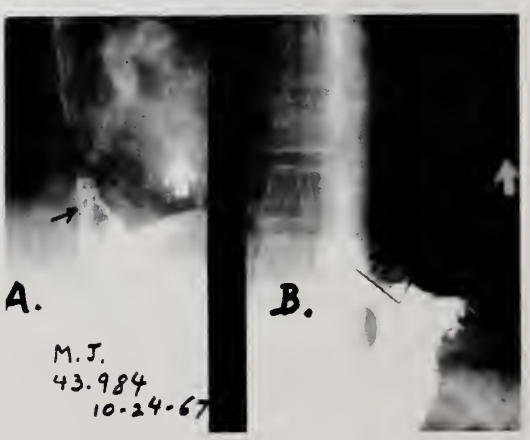


Fig. 8: Case 1. The film was taken in the *erect* position. A: suggests that the hernia is fixed (not sliding), corresponding to type 1 of Akerlund; today we call it HH *with shortened esophagus.* B: the His' angle is 75 degrees which normally is below 50 degrees.

Case 2:

This patient had gall bladder disease with stones and was told that he had diaphragmatic hernia; he had no heartburn. The Fig. 9 shows indeed a typical case of paraesophageal hernia, best seen in the supine position which clearly demonstrates that it is located to the left of the esophagus. It can imitate the sliding type of hernia in the routine prone right oblique positions. The paraesophageal hernias are also called parahiatal hernias (1, 11, 24): they are relatively rare: 5 to 10 percent of the HH (1, 14, 19, 29); they can be quite large and frequently fixed; they are usually symptomless because they are not associated with reflux. They are liable, however, to develop such complications as incarceration or volvulus which may require emergency surgery (29, 15).

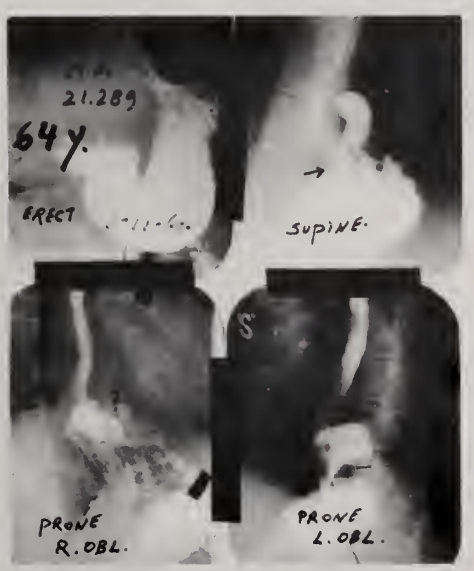


Fig. 9: Case 2. This is a composite picture of 4 different positions for *paraesophageal hernia. Erect:* the distal end of the esophagus is well below the left hemidiaphragm. *Supine:* the hernia originates to the left of the esophagus (most probably through a separate opening in the diaphragm: *parahiatally.)* Prone, right oblique (left shoulder raised), there is overlapping of the esophagus and the hernia; in this "routine" view, it is impossible to differentiate it from a sliding HH. Prone left oblique: is helpful because it shows that the hernia is anterior to the distal end of the esophagus.

Case 3:

Fig. 10 represents the so-called Schatzki's ring (26). Usually there is no reflux, thus no pyrosis; this particular patient was completely asymptomatic. Of course, when the ring is tight, it may cause episodic aphagia: after swallowing a large piece of meat, the patient experiences sudden and complete esophageal obstruction; for this reason, it has been aptly called "steakhouse syndrome" (25). The exact nature of the Schatzki's ring, also called lower esophageal web is still controversial; Harris is against calling it a hernia (17) and Sealy considers it a "semantic and surgical enigma" (27).

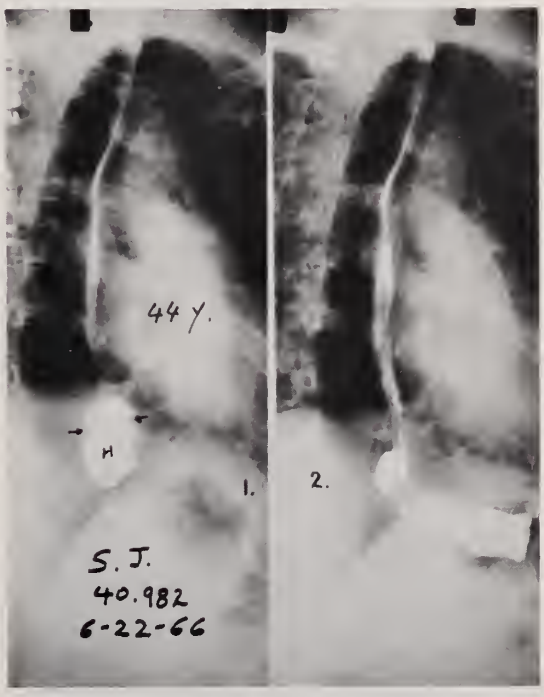


Fig. 10: Case 3. The *Schatzki's ring.* For its demonstration, it is essential that the esophagus be fully distended with barium. Our method of taking a film while the patient drinks thin barium continuously, achieves this: the symmetrical notches (the "ring") are produced in the same manner in all examinations done subsequently.

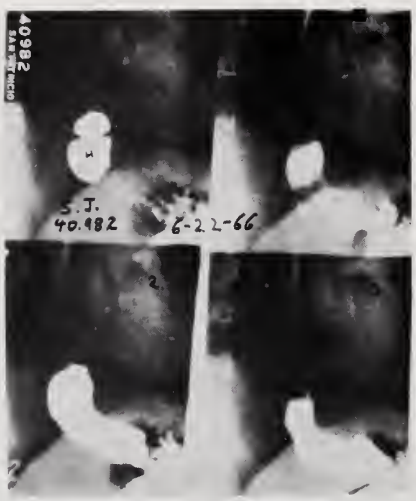


Fig. 11: Case 3. Polygraphic study with thick barium. The ring is shown in only one of the views (upper left). In the other 3 views, the appearance is that of an ordinary sliding hernia.

Case 4:

This patient had heartburn and epigastric pain. Fig. 12 reveals a wide hiatus. The polygraphic study (Fig. 13) demonstrates a small hernia which on a previous examination was called paraesophageal hernia (ot course, erroneously). The important thing is, however, the massive free reflux, documented by the Fig. 14.

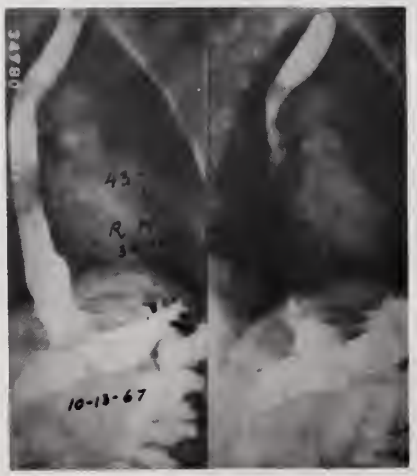


Fig. 12: Case 4. Wide hiatus.



Fig. 13: Case 4. Polygraphic study: A small HH, seen only in the left lower view (arrow).

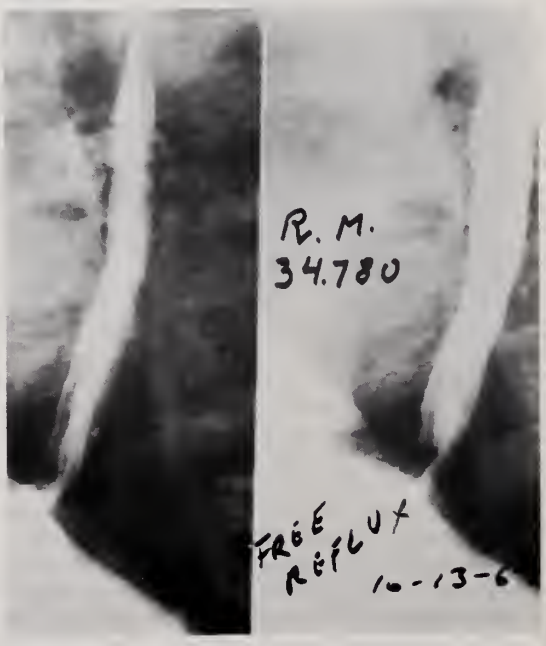


Fig. 14: Case 4. Massive free reflux.

Case 5:

The main complaints were dysphagia and vomiting without heartburn. Fig. 15 shows a normal hiatus. There is evidence of reflux, however (Fig. 16). When the routine 2 sets of polygraphs failed to demonstrate hernia, the patient was submitted to Wolf's maneuver (41) of using a bolster to increase the abdominal pressure; no success: no hernia (Fig. 17). This case demonstrates that one can have reflux without X-ray manifestation of HH. We had several similar cases in the past 6 months.



Fig. 15: Case 5. Normal hiatus.

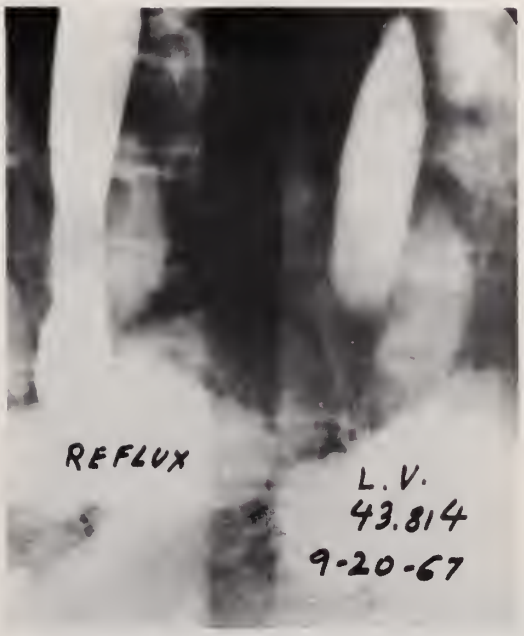


Fig. 16: Case 5. Massive free reflux.

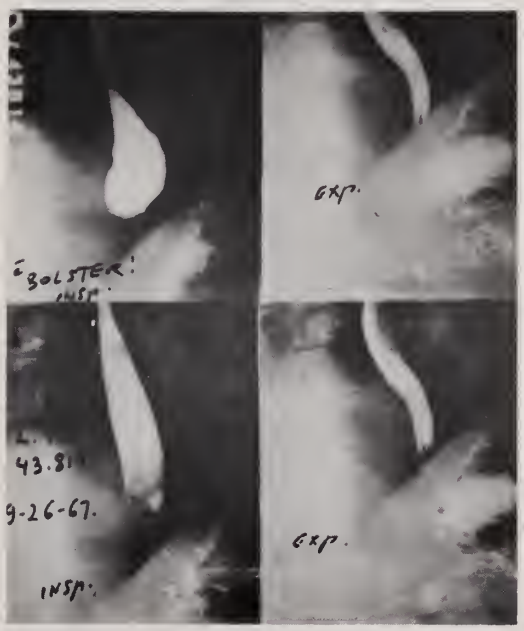


Fig. 17: Case 5. Polygraphic study with *Wolf's maneuver:* using a bolster to increase the abdominal pressure. No HH is demonstrated.

Case 6:

This patient had occasional dysphagia and "hyperacidity". Fig. 18 suggests notches and a questionable widening of the hiatus. He was recalled and the study was repeated; this time the hiatus was normal and there were no notches (Fig. 19). He had no free reflux but induced reflux could be obtained by the water siphonage test (Fig. 20). It is difficult to evaluate this case on the X-ray findings alone. Unquestionably, cineradiography or manometric study could solve the problem.

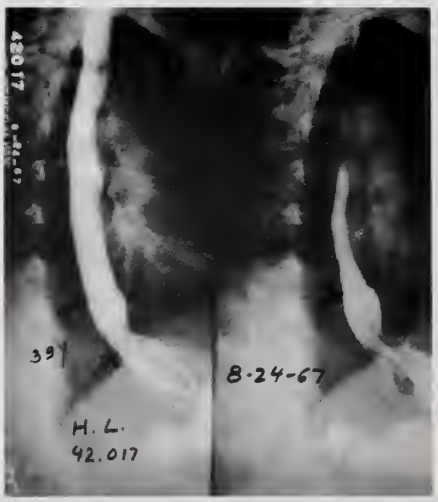


Fig. 18: Case 6. Questionable widening of the hiatus (lower arrow) and suggestion of two shallow notches a few cm. above the hiatus (upper arrows).

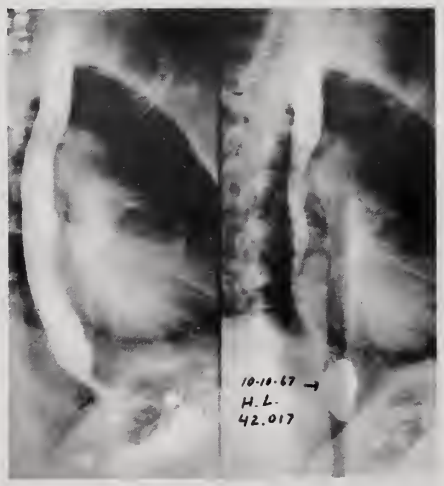


Fig. 19: Case 6. Normal hiatus and no notches. In the right half of the film, there is the phrenic ampulla phenomenon because the patient took a deep breath. (This film is taken routinely in apnea).



Fig. 20: Case 6. Induced *water siphonage test.* The position is the same as for free reflux: *Supine*, with the left shoulder raised. The patient is given a container with 150-200 cc of water which he drinks rapidly thru a large bore sipper. If the test is positive, the barium will erupt into the esophagus; of course, the barium column will be less dense because it is mixed with water. A short and narrow streak of barium is not accepted as a positive test. Again, there is ample time to take several spot films.

Case 7:

According to the X-ray request, the clinical picture was typical of duodenal ulcer, thus only an upper G. I. study was asked for. This revealed no duodenal ulcer but showed the presence of a small HH, as seen in the polygraphic study (Fig. 21). That time, in 1963, he was not tested for reflux. His clinical picture was re-evaluated by the chief of the Surgical Service: the patient admitted having dysphagia and heartburn. He was operated and the study done in 1966 shows no hernia (Fig. 22); had no reflux and complained only of minimal dysphagia.



Fig. 21: Case 7. Polygraphic study. A small HH is obvious.

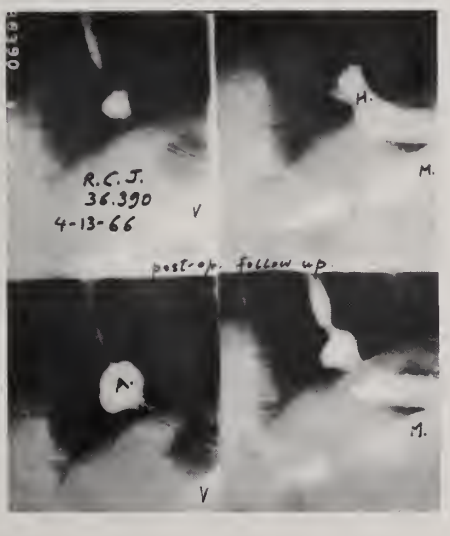


Fig. 22: Case 7. Post-operative check-up. The polygraphic study no longer shows the hernia. That time (in 1966) we still used the Valsalva maneuver which frequently produced the phrenic ampulla phenomenon ("A"); on the other hand, the Muller maneuver was suggestive of persistence of a small hernia...("H"). Since then, we have abandoned these maneuvers: we take the films in inspiration and in expiration.

Case 8:

This case shows the most dreaded complication of HH: stricture formation with ulcer and suspicion of carcinoma. He had retrosternal pain and dysphagia, thus he had to be explored. The resected suspicious segment was free of malignancy (Fig. 23). It is of interest that this patient was treated in our hospital for genito urinary trouble in 1960; because of vomiting he had an upper G.I. study at that time which was "negative except for a moderate sliding hernia". When he was explored in 1964 he also had vagotomy and pyloroplasty. In spite of this, he had several readmissions because of periodic obstruction. He is getting on quite well, however, with dilatations (Fig. 24).

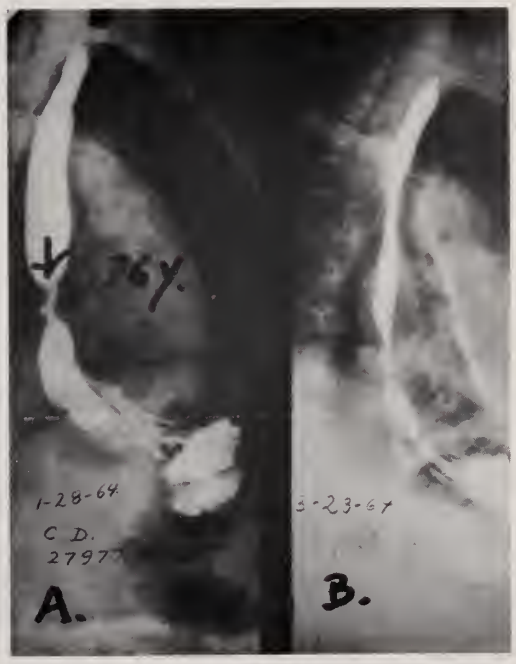


Fig. 23: Case 8. The esophagus is markedly shortened (arrow) showing a stricture and an ulcer. B: Post-operative check-up; no more ulcer and the barium seems to flow easier thru the stricture (at the esophagogastric junction).

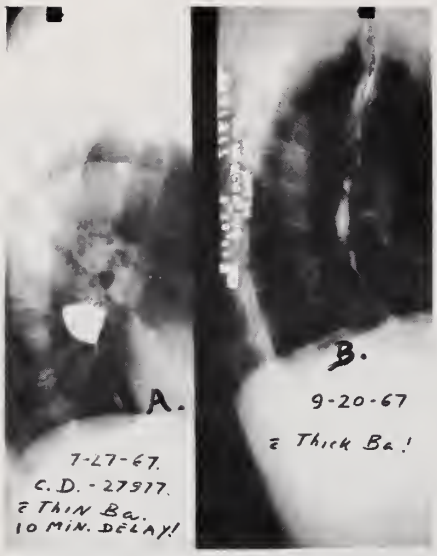


Fig. 24: Case 8. A: re-examination 3 years later shows almost complete obstruction to thin barium. B: after dilatation therapy the obstruction has been relieved; thick barium passes thru without delay!

Discussion

Hiatal hernia is a very complex problem and also controversial in almost every respect including manometry (17), except one: the importance of the reflux. For some mysterious reason, the reflux may be absent one day and present another day (Case 1). This unpredictable behavior of the reflux applies not only to the X-ray examination but also to the endoscopy, since according to Spiro (31), the observation of reflux is more frequent at X-ray examination than by esophagoscopy; according to Dagradi, the reverse is true (9). As to esophagitis, which is often the deciding factor for operation (13), I would like to quote from Ballem: "Experienced endoscopists admit that visual impressions are incorrect often enough to make endoscopic biopsy of fundamental importance" (2). The present controversy is amongst the surgeons concerning indications for operation, operative technics, and results of surgical treatment (10, 19, 30). Although both Harrington (16) and Allison (1) reported a 3 percent post-operative recurrence rate, according to Hill the figure varies between 12 to 58 percent (19). It is very important to realize that the recurrence is not meant in the anatomical sense. As a matter of fact, "any operation which cures the hernia without stopping reflux is a failure" (4). For this reason, the X-ray demonstration of reflux assumes special importance. Whenever free reflux is absent, the induced reflux, called "water siphonage" test should be carried out (5, 36). This test was introduced by Carvalho, a Portuguese surgeon, in 1951. It was popularized in USA by Linsman in 1965 and by Crummy in 1966. They found a good correlation of a positive siphonage test and clinical pyrosis in a large series of upper G. I. studies (8, 23). It is of clinical interest that the patients suffer more while lying on the right side (1): in the very position in which the reflux is best demonstrated. Reflux obtained by abdominal pressure (3, 7) should not be accepted in my opinion because it is due to force and not to physiology; after all, no patient with HH will press on his stomach to cause a painful reflux. Incidentally, the classic position of Trendelenburg for HH and reflux is not considered useful any more (22, 28, 32, 34, 37). In my experience the other 2 tests (Johnstone's touch-toe and Boyd's leg-raising maneuvers) also proved fruitless (21, 28). If we concentrate on the demonstration of reflux, we will find it less embarrasing to learn that in about 10 percent of 640 operated cases the HH was not seen by X-ray, reported by Hiebert (18). The reverse situation also can occur: Fleshler compared manometric studies and X-ray examinations in 21 patients in whom

the diagnosis of HH was made by X-ray; in 13 patients the diagnosis of HH was not confirmed by manometry (12). Those small, so-called grade I hernias can be very elusive on the one hand and can be mimicked by a relaxed (dilated) vestibule on the other hand. Since most of them are asymptomatic, we could consider them as anatomic abnormalities in the same manner as colonic diverticula, of no clinical significance, except for their potentiality to become important. When these small hernias are associated with heartburn, retrosternal pain, etc., these symptoms are not caused by the small hernia in a mechanical sense; they are due to reflux causing esophagitis with all the possible complications: ulcer, bleeding, stricture, etc. The concensus seems to be that the small hernias are the trouble makers. In this respect, it is important to take cognizance of a study made by Vandervelde of the Mayo Clinic. In analyzing 51 cases of reflux encountered in 500 consecutive upper G. I. studies, he found that the reflux were associated with 42 cases of small hernias and 8 of medium size hernias and not a single case of reflux with large HH (37). On the other hand, in Tumen's series of HH, 76 percent of them were classified as "grade I" hernias. According to Templeton, these "grade I" hernias actually may represent a normal anatomic feature...(35).

We radiologists must keep in mind the statement made by Skinner and Belsey: "A radiological report of "no hernia seen" in a patient with typical symptoms of reflux is of little value to the clinician" (29).

The cases reported above are samples of the problem concerning the HH.

Conclusion

In the controversial problem of the HH, its X-ray demonstration is of secondary importance. *The crux of the matter is the demonstration of the reflux*, and the secret of finding it is to look for it.

Summary

The literature on hiatal hernia and esophageal reflux is reviewed. Illustrative cases of the author's material are presented. The author concludes that the clinically significant finding is that of esophageal reflux. Hiatal hernia per se is not clinically important.

Resumen

Se repasa la literatura médica sobre hernia del hiato. El autor presenta una serie de casos para ilustrar sus puntos de vista. Concluye que desde el punto de vista clínico, lo importante es el reflujo esofájico y no la hernia como tal.

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PUBERTAD PRECOZ ASOCIADO A EPILEPSIA TEMPORAL

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El presente artículo tiene como finalidad presentar una entidad nosológica definida, que titulamos "Sindrome de Pubertad Precoz Asociado a Epilepsia Temporal" y que se basa en la presentación de un caso clínico recogido por nosotros, así como también en las aportaciones investigativas y estudios ya realizados, recogidos en la literatura médica mundial.

Resumen Clínico

Paciente mulata de 9 años de edad que nació tras gestación y parto normales. Se desarrolló normalmente y a la edad de dos años y ocho meses sufrió una meningitis purulenta que ocasionó crisis convulsivas generalizadas, permaneciendo hospitalizada durante 22 días, con un cuadro febril que resistió a los antibióticos.

A los cinco años, la madre notó en la niña un desarrollo progresivo de las mamas y dos años después comenzó a menstruar irregularmente y desarrolló hipertricosis en las regiones axilar y púbica. La niña fue hospitalizada para estudios endocrinológicos y luego atendida en la clínica externa del Hospital de Distrito de Bayamón. No se encontró causa endocrinológica que explicara su condición.

Trabajo presentado durante el Primer Congreso Panamericano de Neurología en Lima, Perú, Oct. 1963.

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Alrededor de los 7 años y medio comenzó a tener episodios de mareos y estados oníricos acompañados de disartria e incoherencia, y se quejaba de dolores de cabeza que precedían o seguían a dichos estados oníricos.

Sus compañeros de estudios notaron que en la escuela la paciente tenía episodios en los cuales se veía obnubilada, y ocasionalmente le aparecían crisis incontrolables de risa, existiendo amnesia total para dichos episodios. Por las noches, y con frecuencia, sufría de crisis convulsivas tónicas y posturales que la madre interpretaba como "episodios de excitación". Durante este último año tanto las crisis convulsivas como la menstruación cesaron.

No existían antecedentes familiares de epilepsia, retardo mental, defectos heredo-familiares o pubertad precoz. La madre era de estatura promedio y no presentaba endocrinopatías.

El examen realizado a la edad de 9 años mostró que la paciente tenía una estatura de 4 pies 7 pulgadas, presión arterial 80/58 mm Hg, pulso 90/min., peso 84 libras, tenía abundante pelo púbico y mamas desarrolladas moderadamente. No se constató ningún otro defecto físico ni neurológico.

Los estudios realizados de orina, examen de heces urea en sangre, recuento globular, hemoglobina, serología, glucosa en sangre y radiología de cráneo y de pecho eran normales. La "edad ósea" determinada por radiografías de las manos y antebrazos era compatible con una edad de diez años.

La consulta endocrinológica demostró que el análisis de los 17 cetoesteroides y de los hidroxiesteroides estaban dentro de los límites de la normalidad. El examen ginecológico no mostró anomalías de los genitales externos ni del clítoris, que era de tamaño normal. Por el examen rectal el útero aparecía pequeño, pero no se constató la existencia de tumoraciones o anomalías. La citología vaginal era fisiológica. La evaluación psicológica informó un

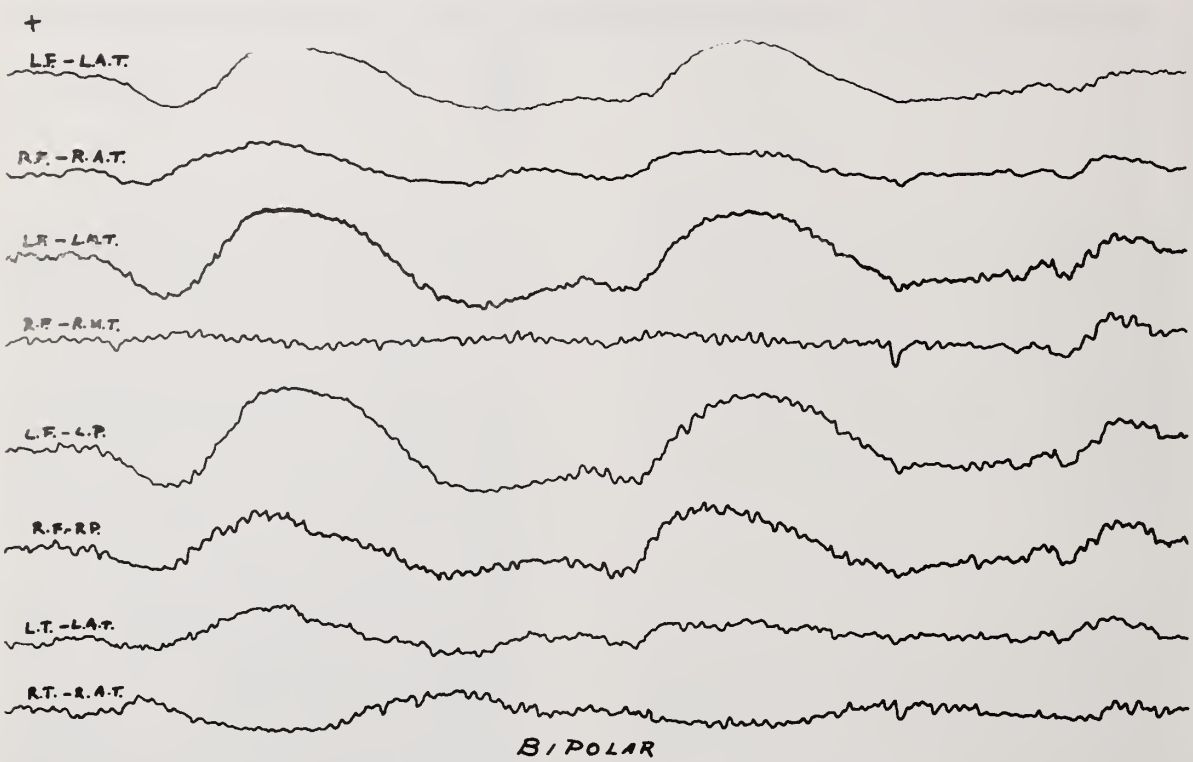


Fig. 1: Porción del trazado electroencefalográfico practicado en un electroencefalógrafo Grass. Lectura con arreglo bipolar, calibración "standard", 50 microvoltios por aplicación de 7 mm. Nótese descargas de ondas agudas en temporal medio derecho.

cociente de inteligencia de 70 interpretado como fronterizo o de ligero retardo mental. Se describió su personalidad como inmadura, con reacciones emocionales lábiles y un ego débil con marcada introversión.

El electroencefalograma señalaba frecuentes descargos de espigas y ondas agudas en el hemisferio derecho, pero particularmente en el lóbulo temporal de dicho lado (Fig. 1, 2).

Se practicó un neumoencefalograma con resultados negativos (Fig. 3, 4, 5). La paciente recibió tratamiento en nuestra clínica externa hasta controlar sus crisis epilépticas y luego fue dada de alta al Centro de Salud de su comunidad.

Comentarios

Tan solo y brevemente daremos las normas que seguimos para considerar a un paciente como precozmente púber. Levine y colaboradores (1) citando a Talbot, dividen la pubertad precoz en isosexual en relación al sexo vero del paciente, y heterosexual, en relación a la adquisición de características del sexo opuesto. Seckel (2) considera la maduración sexual como precoz cuando aparece en varones antes de los diez años y en hembras antes de los ocho años, todo ello claro está, sujeto a variaciones geográficas y raciales.

En el Primer Congreso Internacional de Ciencias Neurológicas que se celebró en Bruselas en el 1957, se presentaron tres casos de epilepsia temporal asociados a endocrinopatías. A-

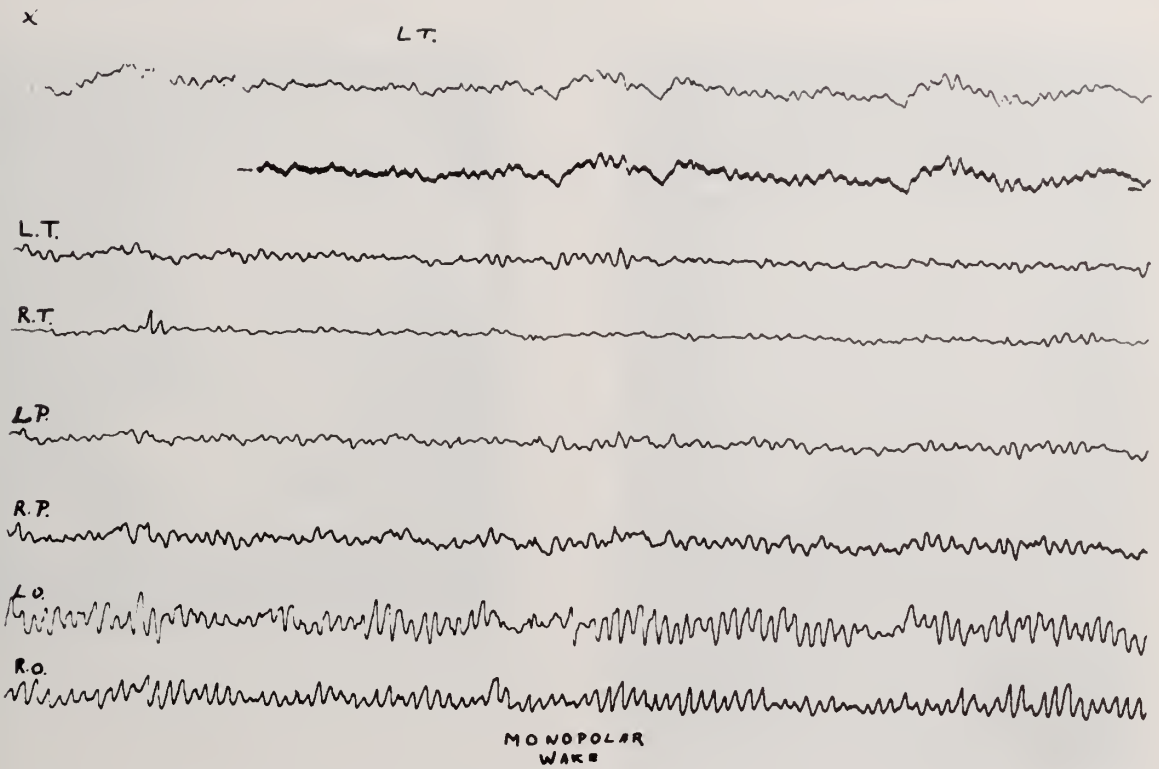


Fig. 2: Porción del trazado electroencefalográfico. Lectura monopolar, sujeto despierto con calibración "standard". Nótese descarga en punta en el área del ilustrado temporal medio derecho.

nastasopoulos y colaboradores (3, 4, 5) habían informado estos casos en diciembre de 1954 a la Sociedad Médica de Salónica, apareciendo publicadas en las revistas médicas griegas, en Julio de 1959. De acuerdo con los autores, estos casos fueron los primeros descritos en la literatura médica, y los primeros que relacionaron las funciones del lóbulo temporal con trastornos sexuales-genitales en el ser humano. Tampoco podemos dejar de señalar los trabajos experimentales de Kluver y Bucy (6, 7, 8, 9) sobre el comportamiento sexual del mono tras la lobectomía temporal bilateral.

El primero de los casos presentados por Anastasopoulos y colaboradores era el de una mujer de 16 años, con antecedentes de un desarrollo precoz de las mamas y pelo púbico a la edad de 5 años y que tuvo su menarquía a los 5 años y medio. A la edad de once años desarrolló crisis epilépticas de tipo psicomotor, que solían presentarse unos días antes o después del período menstrual. El examen de ingreso realizado en la clínica de Neurología y Psiquiatría de la Universidad de Atenas y los estudios practicados posteriormente revelaron los siguientes hallazgos: Paciente de baja estatura, (cuatro pies con tres pulgadas) su cociente de inteligencia normal. El examen neurológico no reveló patología alguna, excepto el neumoencefalograma practicado el

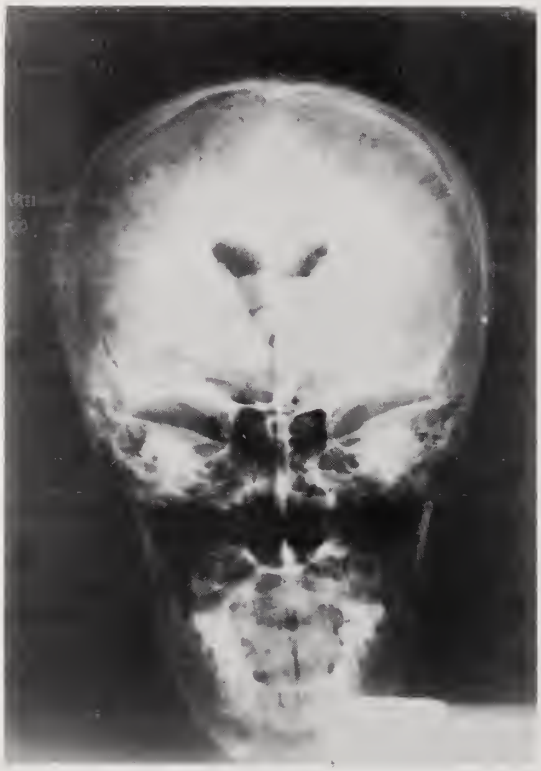


Fig. 3: Proyección postero-anterior de la neumografía practicada en el caso que se informa. Nótese tamaño normal y simétrico del sistema ventricular. El ventrículo lateral derecho tiene línea de líquido cefaloraquideo sin vaciar.



Fig. 4: Proyección lateral que demuestra el sistema ventricular izquierdo. Nótese el tamaño normal particularmente el cuerno temporal.



Fig. 5: Proyección lateral-posterior derecha que demuestra tamaño normal del sistema ventricular con un cuerno temporal derecho normal.

cual mostró una dilatación ligeramente hidrocefálica del sistema ventricular, con una marcada dilatación del cuerno temporal derecho. Cinco años más tarde la paciente murió debido a una cardiopatía super-impuesta. El post mortem mostró la existencia de tuberculosis del ovario derecho y atrofia cerebral con dilatación del cuerno temporal derecho.

El segundo caso, era de una niña de tres años que había tenido una crisis convulsiva

durante un estado febril a la edad de seis meses. A la edad de un año tuvo un desarrollo anormal de las mamas, y al año y medio, después de otra crisis convulsiva, comenzó a menstruar. A los dos años había desarrollado ya pelo púbico y sus crisis semejaban episodios de excitación psicomotora. El examen físico y neurológico no mostró anomalías excepto el desarrollo prematuro de las mamas, y la existencia de pelo púbico ya señalados, así como también por un lunar melanocromático en el muslo izquierdo. Un electroencefalograma practicado, reveló la presencia de descargas epileptogénicas en el hemisferio izquierdo, particularmente, en el área temporal izquierda, asociados a ritmos lentos, lo cual sugería la existencia de áreas atróficas. No se practicó neumoencefalograma en este caso.

El tercer caso citado se trataba de una mujer de 19 años, que a los siete había comenzado a sufrir episodios de agitación con movimientos involuntarios de las extremidades, seguidos de amnesia. A los 16 años la paciente desarrolló un comportamiento psicótico originándose entonces un problema médico-legal, ya que apuñaló a un primo que supuestamente la había violado. En el examen físico la paciente presentaba discreta hipertricosis mentoniana, así como pelo abundante en axila, cuello, pecho y muslos. Los estudios de laboratorio demostraron un defecto de la actividad folicular, así como también ausencia de ovulación. Los electroencefalogramas practicados revelaron un ritmo alfa de bajo voltaje en el lado derecho, con ondas lentas de 4 por segundo en las regiones rolando-occipitales y temporo-occipitales. Un neumoencefalograma demostró una dilatación marcada del cuerno temporal del ventrículo derecho.

Así pues, los autores nos presentan dos casos de pubertad precoz y un tercero de virilismo, todos asociados a epilepsia temporal; de hecho no encontraron causa aparente que explicara la dilatación del cuerno temporal ni tampoco lesiones que explicaran el cuadro endocrino. La tuberculosis del ovario encontrada en el primer paciente no explicaba la pubertad precoz, la cual precedió por cinco años a la aparición de las crisis psicomotoras. En el segundo caso, una condición febril pudo haber causado la atrofia temporal. Las crisis psicomotoras antecedieron aquí a la pubertad precoz por un año. La diferencia entre los primeros dos casos y el tercero presentado por los autores podría explicarse por alteraciones constitucionales, somáticas y endocrinas.

Los autores relacionaron el cuadro endocrinológico con la epilepsia temporal y presentaron pruebas a favor de dicho concepto, consistentes en estudios aparecidos previamente en la literatura médica mundial.

Westphal (10) en el 1918 fue el primero en informar la relación existente entre un cuadro de endocrinopatía y epilepsia. La epilepsia por él descrita era de tipo mioclónica centroencefálica y la lesión endocrina la de distrofia adiposogenital.

Masson y Roger (11) citaron por primera vez la relación entre crisis convulsivas y la presencia de pubertad precoz. A este informe siguieron los trabajos de Lange-Casack (12, 13), Giraud (14), Grabes (15), Stutte (16), y recientemente los de Scherman y Abraham (17), relacionando el cuadro de pubertad precoz con epilepsia centroencefálica.

La evidencia en favor de la relación que pueda tener la actividad epileptiforme bien sea de origen centroencefálica, psicomotora, o una lesión rinencefálica con cuadros endocrinológicos está extensa y adecuadamente reflejada en los trabajos de Anastasopoulos y colaboradores (18, 19), y debe referirse el interés del lector a los mismos. En estos trabajos

se informan los tres casos señalados de epilepsia temporal con endocrinopatía y además un caso de sumo interés, el de un paciente con epilepsia psicomotora que desarrolla episodios transitorios de bulimia, anorexia e hipersexualidad tras practicarle una neumografía.

Son así mismo de gran interés los trabajos sobre el sistema límbico, y lóbulo temporal, trabajos que han pasado a ser material clásico en el campo de la neuroanatomía y neurofisiología, que tratan de las anomalías sexuales tras realizar oblaciones experimentales de las regiones temporales con respuestas de mansedumbre, respuestas hipersexuales, estro y otros; interesantes son también las estrechas relaciones con hipocampo, amígdala y otras estructuras rinencefálicas de sobras conocidas. Es así mismo digno de recordar que aparte de estas regiones intimamente relacionadas, su proximidad hace que dichas áreas estén frecuentemente envueltas en su mismo proceso nosológico.

Resulta loable un último trabajo presentado por Wolman y Balmforth (20) los cuales discuten un caso de pubertad precoz secundario a un hamartoma sito en la región hipotalámica, con abundantes datos anatomofuncionales.

Es algo difícil para nosotros explicar la relación que pueda existir entre la epilepsia temporal por lesión de uno de los lóbulos temporales y el cuadro endocrinológico que presentaron los casos de Anastasopoulos y el nuestro. Nuestro caso se parece a los de pubertad precoz por ellos presentados, con la diferencia que no se encontró atrofia del lóbulo temporal con dilatación del cuerno temporal del ventrículo. En nuestro caso pequeñas zonas de gliosis postmeningíticas pudieron ser la etiología del foco epileptogénico. Esto sugiere una de dos cosas: o que en nuestros casos la epilepsia temporal es coincidental, y no relacionada a un cuadro de pubertad precoz, o que la atrofia del lóbulo temporal no es requisito para que ocurra el sindrome. En tal caso, había que atribuirle a la actividad epileptogénica la capacidad de provocar el trastorno endocrino. No podemos tampoco, pasar por alto los clásicos trabajos de Karle, Baldwin y Penfield (21) sobre la herniación hipocámpica como consecuencia del trauma del parto y el resultante cuadro de epilepsia temporal. Presenta serias dificultades explicar el hecho de que en el tercer caso de Anastasopoulos y colaboradores la endocrinopatía se manifestó por virilismo y no por pubertad precoz con hallazgos electroencefalográficos y de pneumografía similares. ¿Sería aceptable la explicación de que se debe a diferencias constitucionales y endocrinológicas? No podemos decirlo.

Podemos asumir al igual que Anastasopoulos que la causa de la pubertad precoz en los casos informados reconocen una lesión en uno de los lóbulos temporales, y por ende se alteran las funciones hipotalámicas. A favor de este concepto están los estudios de Kluver y Bucy (6, 9), Green (22, 23), Gastaut (24, 25, 26), Petit - Dutaillis (27), Sawa (28), y Terzian (29), que relacionan ananatomofuncionalmente la región rinencefálica, hipotálamo, sindromes endocrinas y/o anomalías sexuales. La estimulación eléctrica de regiones rinencefálicas, tal y como se puede apreciar en los trabajos de Haterius (30) y Wood (31) así como las observaciones clínicas observadas por Anastasopoulos (32, 33), Thompson (34), Gastaut y Collomb (24) y Van Reeth (35), apoyan la posible relación existente entre las lesiones temporales y/o rinencefálicas con diversos cuadros endocrinos de naturaleza hoy por hoy todavía bajo intensa investigación.

Summary

A case of precocious puberty associated with temporal lobe epilepsy is reported. The patient was a nine year old girl with precocious puberty who also had temporal lobe epilepsy proven by electroencephalography.

A pneumoencephalogram in this case failed to show the temporal lobe atrophy reported in the cases of Anastasopoulos and his group.

The medical literature is reviewed, the anatomical and physiological basis of this syndrome are discussed.

Resumen

Se informa un caso de pubertad precoz asociado a epilepsia temporal. La paciente era una niña de nueve años con un desarrollo prematuro iso-sexual que padecía de ataques de epilepsia temporal comprobados por electroencefalograma.

Un neumoencefalograma practicado en esta paciente no acusó atrofia lóbulo temporal en contraste con los casos informados por Anastasopoulos y su grupo.

Se resume la literatura médica sobre este tema y se comenta sobre las bases anatómicas y fisiológicas de este sindrome.

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Dyslexia

A disorder in children, who, despite conventional classroom experience, fail to attain the language skills of reading, writing and spelling commensurate with their intellectual abilities.

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN PUERTO RICO

A Review

M. R. García Palmieri, MD

Puerto Rico is a tropical island with an area of 3,400 square miles located between parallels of 18 degrees and 19 degrees North latitude. The average elevation of the mountains is 800 feet with a maximum elevation of 4000 feet. The mountainous area extends across the island from the northeast to the southwest corners. The mean temperature for the entire island is 73.9 degrees in the winter and 79 degrees in the summer with an average temperature of 76.8 degrees. The mean relative humidity for San Juan city in the northern coast is 86 percent at 2:00 AM and 66 percent at 2:00 PM. The mean relative humidity for the city of Ponce in the southern coast is 82 percent at 2:00 AM and 62 percent at 2:00 PM (1). Although diurnal variations are present there are no stricking seasonal variations in relative humidity.

The study of the problem of rheumatic fever (RF) and rheumatic heart disease (RHD) in Puerto Rico has been limited, as in other countries of the world, by the lack of epidemiologically oriented studies about this disease. Most of the information available has been obtained from selected groups in the population.

It is the purpose of this paper to review the information available concerning this illness in Puerto Rico. A perusal of the literature was conducted and an analysis of the available data was made. The information obtained consists mainly of admissions of ambulatory patients to cardiac clinics, admissions to hospitals, experience of private and government employed physicians, autopsy studies and the vital statistics from the Bureau of Demographic Registry of the Department of Health of the Commonwealth of Puerto Rico.

The first confirmed case of rheumatic fever, with Aschoff's bodies, was encountered by Dr. Hans Smetana on June 28, 1930 when he performed an autopsy in a 15 year old Puerto Rican boy (2). The first publications with reference to rheumatic heart disease were presented by Suárez in 1945 (2) and Francisco in 1946 (3). Since then, different local investigators have written primarily about the problem of rheumatic fever and rheumatic heart disease (4-9) and others while writing about heart disease have included valuable information about rheumatic heart disease (10-12).

Francisco encountered RHD in 20 out of 1,373 freshman students at the University of Puerto Rico in 1946. Suárez stated in 1945 that out of 31,600 selectees for military service 1.5 percent were found to be suffering from heart disease, most of them due to rheumatic heart disease.

Forty out of 10,388 medical admissions at the Bayamón District Hospital during the years 1939-1943 were patients with RHD for a figure of 0.4 percent. Rheumatic heart disease was responsible for 25 percent of the

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total of 160 cardiac patients admitted during that period (3).

At the Arecibo District Hospital 5,000 patients were admitted to the medical service from 1941 to 1943 and fifty patients were proven to have RHD, a figure of 1 percent. Rheumatic heart disease was responsible for 30 percent of the total of 150 cardiac patients (3).

The lack of a specific laboratory test for confirmation of rheumatic fever has caused difficulty in getting uniformity for the establishment of a definite diagnosis in this illness. In Puerto Rico the utilization of the modified Jones' criteria recommended by the American Heart Association has had island wide acceptance in the cardiac clinics and major hospitals.

The clinical diagnosis of RHD can be established with reasonable certainty taking into consideration the history, findings on physical examination, electrocardiogram and roentgenogram. Cardiac catheterization and angiography add further diagnostic reliability. The post mortem anatomic diagnosis of rheumatic heart disease is more reliable. Unfortunately autopsies are not done on all the deaths and the figures obtained represent the findings encountered in those cases where the procedure was performed. Nevertheless this is a most valuable data if the limitations of the selection of material is understood.

An analysis of the published autopsy data from Puerto Rico presenting the cardiac deaths and the percentage of cardiac deaths due to RHD and other etiologies is summarized in table I (2, 10, 11). The data on 3600 consecutive autopsies previously unpublished, as analyzed by Galindo from the School of Medicine of the University of Puerto Rico, are also included in that table (13).

Although RHD was responsible for 20 per-

TABLE I: AUTOPSY STUDIES INCLUDING TYPES OF CARDIAC DEATHS

	School of Tropical Medicine		School of Medicine (13)		Ponce District Hospital		San Juan City Hospital	
	Until 1944		1958-61		1956-62		1955-63	
Total autopsies	1259		3600		2000		2131	
Cardiac deaths (CD)	128		871		415		431	
	Deaths	*Percentage CD*	*Deaths*	*Percentage CD*	*Death*	*Percentage CD*	*Death*	*Percentage CD*
Arteriosclerotic	22	17.0	673	77.2	133	32.0	216	50.1
Arteriolosclerotic	12	9.3	--	--	--	--	--	--
Arteriosclerotic & Hypertensive	--	--	--	--	53	12.8	--	--
Hypertensive	--	--	--	--	41	9.9	45	10.5
Rheumatic	26	20.0	73	8.4	32	7.7	34	7.9
Congenital	10	7.8	--	--	83	20.0	81	18.8
Syphilitic	38	30.0	11	1.2	--	--	7	1.6
Others	20	15.7	114	13.2	73	17.6	48	11.1

TABLE II: PERCENTAGE DISTRIBUTIONS OF TYPES OF HEART DISEASE BY CLINICS

	Suárez	San Juan City Hospital	Ponce District Hospital	Mayaguez Health Center	Arecibo District Hospital
	1937-44	1952-62	1959-62	1959 - 62	1959 - 62
Total Cases	1081	2433	919	497	694
Arteriosclerotic	40.0	41.8	44.3	36.4	35.9
Arteriosclerotic & Hypertensive	--	--	6.9	--	--
Hypertensive	22.8	21.7	20.7	12.6	18.8
Rheumatic	17.1	16.2	11.8	10.4	19.8
Congenital	1.0	16.0	11.3	31.7	22.7
Syphilitic	6.1	3.2	1.4	4.6	1.3
Other	10.2	.9	3.5	4.0	1.3

cent of all cardiac deaths in the autopsies of the School of Tropical Medicine in 1944, it has constituted 8.4 percent, 7.7 percent and 7.89 percent of all cardiac deaths in the most recent autopsy studies. In the autopsies performed at Ponce, as well as those by Galindo, RHD constituted the commonest cause of cardiac death for the 10-30 years age group.

The clinical picture of rheumatic fever and RHD in the Puerto Rico adult and children has been described at length. The authors agree that the clinical manifestations of this disease, as it occurs in Puerto Rico, is nearly identical to that reported in the temperate zones of the world and as it is described clasically (4, 5, 8). It is worth noticing that a definite seasonal variation in the onset of rheumatic attacks with predominance in the winter and the spring occurs in our island. In Puerto Rico there are no stricking changes in temperature, rainfall and relative humidity during the different seasons of the year.

The magnitude of the problem of rheumatic heart disease as a cause of clinical heart disease in Puerto Rico can be appraised from the experience obtained in different cardiac centers. Table II summarizes this information as obtained from the published literature. It includes the figures of Suárez from 1937 to 1944 (2), San Juan City Hospital from 1952 to 1962 (11) and Ponce District Hospital (10), Arecibo District Hospital and Mayaguez Health Center from 1959 to 1962. Of 722 male veterans with cardiac disease seen by 1959, RHD occurred in 12.2 percent (14). Rheumatic heart disease was responsible for 10.4 to 19.8 percent of all new cardiac patients seen at those cardiac centers.

Most recent data obtained from all the Heart Disease Control Program cardiac clinics distributed throughout the island is shown in tables III and IV. Table III illustrates the types of heart disease seen in each of the eight cardiac clinics from July 1, 1962 to June 30, 1967. Rheumatic heart disease constituted from 7.9 to 17.2 perecent of all new cardiac patients seen at each clinic with an average of 12.2 percent. These clinics include patients of all ages and both sexes.

Table IV presents the total admissions to

TABLE III: PATIENTS ADMITTED TO EACH CLINIC OF THE HEART DISEASE CONTROL PROGRAM *

Hospital	Cases with H.D.		Types of Heart Disease											
			HHD		As HD		RHD		SHD		CHD		OHD	
	No.	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*
San Juan City	855	100.0	133	15.6	395	46.2	99	11.6	14	1.6	200	23.4	14	1.6
Presbyterian	510	100.0	75	14.7	295	57.8	77	15.1	1	0.2	51	10.0	11	2.2
Aguadilla District	1 652	100.0	216	13.1	825	49.9	245	14.8	--	--	327	19.8	39	2.4
Arecibo District	685	100.0	185	27.0	305	44.6	77	11.2	3	0.4	100	14.6	15	2.2
Fajardo District	857	100.0	178	20.8	419	48.9	89	10.4	--	--	166	19.3	5	0.6
Ponce District	2155	100.0	722	33.5	862	40.0	220	10.2	8	0.4	286	13.3	57	2.6
University District	913	100.0	28	3.1	114	12.5	157	17.2	2	0.2	600	65.7	12	1.3
Mayaguez Health Center	762	100.0	99	13.0	306	40.1	60	7.9	10	1.3	258	33.9	29	3.8
TOTAL	8389	100.0	1636	19.5	3521	42.0	1024	12.2	38	0.5	1988	23.7	182	2.2

HD - Heart Disease; HHD - Hypertensive Heart Disease; ASHD - Arteriosclerotic Heart Disease; RHD - Rheumatic Heart Disease; SHD - Syphilitic Heart Disease; CHD - Congenital Heart Disease; OHD - Other Heart Disease.

** July 1, 1962 to June 30, 1967.*

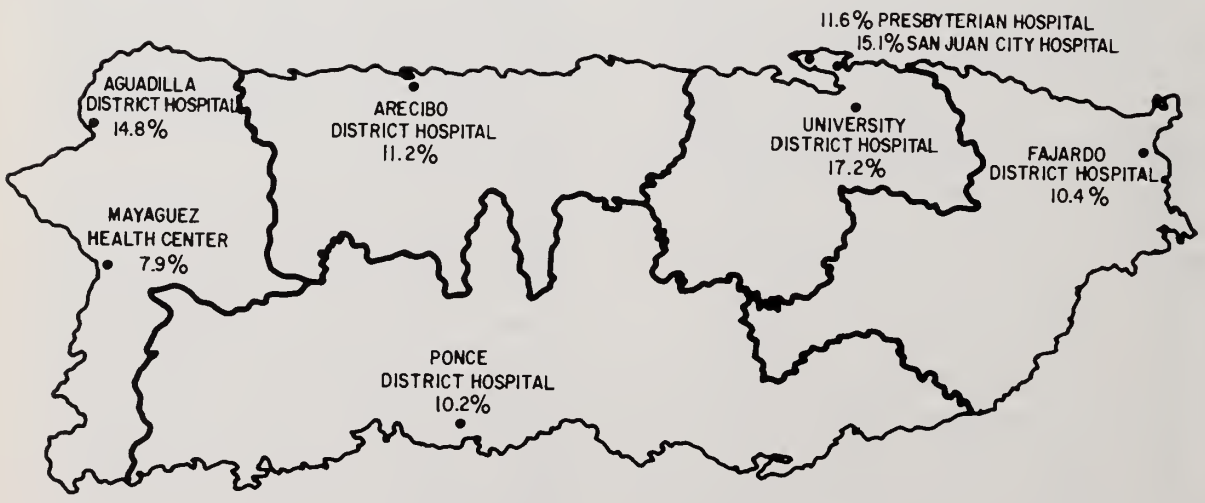


Fig. 1: Percentage of RHD admissions by cardiac clinics for fiscal year 1963-67.

TABLE IV: ADMISSIONS TO HEART DISEASE CONTROL PROGRAM CLINICS

Year	Cases with H.D.		Types of Heart Disease											
			H.H.D.		As.HD		R.H.D.		S.H.D.		C.H.D.		O.H.D.	
	No.	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*	*No.*	*Percent.*
1962 - 63	2089	100.0	323	15.5	1009	48.3	268	12.8	12	0.6	421	20.1	56	2.7
1963 - 64	1601	100.0	309	19.3	651	40.7	184	11.5	8	0.5	426	26.6	23	1.4
1964 - 65	1783	100.0	407	22.8	664	37.2	224	12.6	9	0.5	449	25.2	30	1.7
1965 - 66	1494	100.0	347	23.2	571	38.3	163	10.9	2	0.1	363	24.3	48	3.2
1966 - 67	1422	100.0	250	17.6	626	44.0	185	13.0	7	0.5	329	23.1	25	1.8
Total	8389	100.0	1636	19.5	3521	42.0	1024	12.2	38	0.5	1988	23.7	182	2.2

TABLE V: RF CASES ADMITTED TO THE HEART DISEASE CONTROL PROGRAM CLINICS

Clinic Site	1962-63	1963-64	1964-65	1965-66	1966-67
San Juan City Hospital	11	3	9	3	2
Presbyterian Hospital *	5	4	5	3	--
Aguadilla District Hospital	43	10	12	9	6
Arecibo District Hospital	2	1	5	7	5
Fajardo District Hospital	3	5	7	6	42
Ponce District Hospital	22	15	14	7	6
University District Hospital	--	5	3	15	14
Mayaguez Health Center	3	2	5	2	2
Total	89	45	60	52	77

* *Formerly Río Piedras Municipal Hospital Clinic*

TABLE VI: CARDIAC DEATHS - BUREAU OF DEMOGRAPHIC REGISTRY

Year	Total Deaths	Cardiac Deaths	A S H D		H H D		R H D		Other H D	
			Deaths	Percent. of CD	Deaths	Percent. of CD	Deaths	Percent. of CD	Death	Percent. of CD
1950	21917	2404	1554	64.6	353	14.6	103	4.2	394	16.3
1951	22371	2566	1627	63.4	365	14.2	125	4.8	449	17.4
1952	20504	2498	1638	65.5	409	16.3	87	3.5	364	14.5
1953	17966	2532	1672	66.0	392	15.4	102	4.0	366	14.4
1954	16871	2390	1565	65.4	341	14.2	90	3.7	394	16.4
1955	16243	2352	1450	61.6	401	17.0	79	3.3	422	17.9
1956	16607	2639	1763	69.4	340	13.3	91	3.5	445	17.5
1957	16022	2694	1864	69.1	327	12.1	73	2.7	430	15.9
1958	16099	2655	1834	69.1	394	14.8	68	2.5	358	13.4
1959	15870	2846	2037	71.5	386	13.5	65	2.2	358	12.5
1960	15841	2820	2070	73.4	360	12.7	85	3.0	305	10.8
1961	16361	3197	2274	71.1	389	12.1	105	3.2	429	13.4
1962	16575	3197	2341	73.2	391	12.2	77	2.4	388	12.1
1963	17386	3268	2414	73.9	369	11.3	75	2.3	410	12.5
1964	18556	3484	2562	73.5	411	11.8	95	2.7	415	11.9
1965	17719	3699	2763	74.7	399	10.8	99	2.7	438	11.8
1966	17506	3819	2886	75.5	406	10.6	79	2.1	448	11.7
Total 1950-66	300414	49060	34314		6433		1498		6813	

all the clinics each fiscal year. There was no difference in the percentage of cardiac admissions due to RHD to the eight clinics during the years observed.

In figure 1 the percentage of RHD admissions to all cardiac cases admitted in the different clinics of the Heart Disease Control Program of the Department of Health from July 1, 1962 to June 30, 1967 is shown in order to illustrate the geographical distribution by the 5 health regions.

The Aguadilla and Mayaguez clinics have been serving the western region. The percentage of rheumatics per total cardiac admissions was less in Mayaguez, but if we group together the 1652 cardiacs seen at Aguadilla with the 762 seen at Mayaguez and add their respective RHD cases (305) we obtain a figure of 12.2 percent for the western region. There is no difference in the percentage of rheumatics in the western region as compared to the northern, southern, northeast and eastern regions.

Of 4672 women discharged from the Department of Obstetrics and Gynecology of the University District Hospital, that had a viable delivery, during the period of July 1966 to June 1967, 42 cases had organic heart disease. Among these 25 or 59.5 percent had rheumatic heart disease (15). Rheu-

TABLE VII: BUREAU OF DEMOGRAPHIC REGISTRY - DEATH RATES PER 100,000 INHABITANTS

Year	1950	1955	1960	1965	1966
Cardiac Deaths	104.1	99.7	115.7	136.5	138.1
Rheumatic Heart Deaths	4.6	3.5	3.6	3.8	2.9

matic heart disease as a significant cause of heart failure in pregnant women in Puerto Rico was previously noted (4).

Patients with a clinical diagnosis of RF are frequently referred to the cardiac clinics of the Heart Disease Control Program for management which includes secondary prophylaxis. Table V shows the cases of RF admitted to such clinics for the period of July 1, 1962 to June 30, 1967.

The vital statistics of the Bureau of Demographic Registry of the Department of Health of the Commonwealth of Puerto Rico present considerable information concerning the cardiac deaths in Puerto Rico. We are aware of the limitations of death certificate information but a recent study performed during a 6 month period for validation of death certificates in the San Juan Metropolitan area revealed a rewarding correlation among the death certificate information and the validated data (16).

Table VI presents the total deaths, total cardiac deaths and the deaths by the types of heart disease for all ages for the years 1950 to 1966. Rheumatic heart disease was responsible for 2.1 to 4.8 percent of all cardiac deaths. In no instance since 1961 has RHD accounted for 3 percent or more of the cardiac deaths. Of the total 49,060 cardiac deaths that occurred from 1950 to 1966, 1,498 were due to RHD, that is 3.05 percent of all cardiac deaths. Rheumatic heart disease constituted 0.49 percent of the total of 300,414 deaths that occurred during that period.

Table VII shows the deaths due to cardiac disease and to RHD per 100,000 population for the years 1950, 1955, 1960, 1965 and 1966. Further analysis in coming years will help to decide whether the drop in 1966 is indicative of a trend in reduction in deaths due to RHD. During those years RHD constituted the commonest cause, (43.4 percent), of cardiac deaths for the age groups of 10 to 30 years of age.

Rheumatic heart disease has been one of the leading conditions requiring heart surgery in Puerto Rico. The first commisurotomy was performed by Dr. David Rodríguez on April 1953 at the Bayamón District Hospital (17). Most of the cardiac surgery performed in Puerto Rico in the last years has been done at the University District Hospital. Table VIII shows that 815 cardiac surgical interventions have been performed at this institution since 1959 (18). One hundred and eight (13.2 percent) have been for patients with RHD. Of these, 63 have been open and 45 closed surgery. The open procedures include 34 valve replacements.

At the San Juan City Hospital, RHD was responsible for 3.8 percent of all hospital admissions to the medical service for the years 1952 to 1960. This is higher than the fi-

TABLE VIII: CARDIAC SURGERY AT THE UNIVERSITY DISTRICT HOSPITAL (17)

Year	Patients Operated	RHD Cases
1959 - 60	87	6
1961	97	18
1962	95	10
1963	101	14
1964	55	12
1965	89	6
1966	120	21
1967	151	21
Total	815	108 *

** 63 open heart surgery; 45 closed surgery*

gures offered by Francisco for Bayamón District Hospital and Arecibo District Hospital during the years 1939 to 1943. Table IX shows the hospital admissions due to RHD and RF to the medical and pediatric services of the Ponce District Hospital during recent years (19).

Although RF and RHD undoubtedly constitute a significant health problem in Puerto Rico prevalence data has been unavailable. One such study has been conducted in Puerto Rico (20). This study included a total of 651 apparently healthy sixth-grade students at four public schools in San Juan ranging in age from 10 to 16 years. Five gave histories of having had rheumatic fever. Only one case of RHD was obtained in the 651 sixth grade Puerto Rican school children for an approximate prevalence of 1.5 per 1,000 for the group.

The problem of beta-hemolytic streptococcus has been studied in Puerto Rico at different year intervals (21-26). Tables X and XI taken from Pomales-Lebrón and Bonilla-Soto summarize such studies (21).

Throat cultures from 1490 soldiers stationed in Puerto Rico, 785 continental North Americans who had been on the island for two months to one year, and 705 Puerto Ricans, were carried out in 1943 and 1944 (22). Gross hemolytic carrier rates of 10 percent and 17.4 percent were obtained in continental and Puerto Rican troops respectively. Group A carrier rates of 2.3 percent for continental and 1.2 percent for Puerto Rican were found.

Results of Dick testing in Puerto Rico in 1936 (23) and in 1959 (21) were comparable to those reported in temperate zones. Median antistreptolysin "O" (ASO) values in

TABLE IX: RHD AND RF ADMISSIONS TO THE PONCE DISTRICT HOSPITAL

	DEPARTMENT OF PEDIATRICS					DEPARTMENT OF MEDICINE				
Year	Total Admissions	RHD	Percent	RF	Percent	Total Admissions	RHD	Percent	RF	Percent
1965	2470	4	0.16	7	0.29	2259	63	2.8	14	0.6
1966	2243	2	0.08	8	0.35	1975	40	2.0	8	0.4
1967						2113	39	1.7	9	0.4

TABLE X: GROSS THROAT CARRIER RATES OF BETA-HEMOLYTIC STREPTOCOCCI IN STUDIES DONE IN PUERTO RICO AT DIFFERENT TIMES *

Date	Age	Number Examined	Percent positive	
Sept. 1929	> 15 yrs.	?	10.0	(26.0) **
Mar. 1930	> 15 yrs.	?	4.0	(10.4)
1929 whole year - Highly selected normal persons	> 15 yrs.	200	4.0	(10.4)
1934, whole year (all men)	> 15 yrs.	416	9.0	(23.4)
1944, whole year (all men)	> 19 yrs.	705	17.4	(45.0)
Feb. - Apr. 1959	> 15 yrs.	1076	2.7	(6.2)
May 1959	6-14 yrs.	1145	28.0 ***	

* *Unless otherwise stated, persons representative of general population were examined.*

** *Figures in parentheses represent the calculated percentage if the isolation had been done using Pike's medium.*

*** *Results with Pike's medium.*

serums from 473 Puerto Rican soldiers (73.0 units) and 486 North American troops (69.2 units) stationed in Puerto Rico for two months to one year when determinations were made, did not vary significantly (22). Results of single throat culture studies, using the direct streak and pour plate methods, and ASO determinations in a mixed group representative of the general population showed ASO values comparable to those obtained in temperate zones and to values obtained in previous studies in Puerto Rico (23). The stu-

TABLE XI: CARRIER RATES OF BETA-HEMOLYTIC STREPTOCOCCI AMONG CHILDREN (6 TO 14 YEARS) OF THE SOUTH CENTRAL COASTAL AREA OF PUERTO RICO - APRIL, 1959

Location	Number Examined	Carrier rates		Percent of Group A among positives
		Gross	Group A	
Ponce (rural)	527	27.5 %	7.5 %	27.5
Ponce (urban)	294	24 %	6.5 %	28
Guayama (urban)	212	35 %	10.4 %	28
Guayama (rural) *	112	31 %	20.6 %	66

* *Many with hypertrophic purulent tonsils.*

TABLE XII: IDENTIFICATION OF GROUP A - B HEMOLYTIC STREPTOCOCCI FISCAL YEAR 1963 - 67

Fiscal Year	Total No. Specimens Examined	Number Negative	Number Positive	Per Cent Positive
1963	4313	3562	751	17.4
1964	6152	5503	649	10.5
1965	6284	5727	557	8.8
1966	6498	5930	568	8.7
1967	4571	4266	305	6.6

dies on school children show that Group A hemolytic streptococci are commonly encountered in Puerto Rico (21).

The Heart Disease Control Program of the Department of Health has laboratory facilities for identification of Group A hemolytic streptococcus that are available to all the physicians practicing in Puerto Rico. Swabs and the laboratory service are provided free of cost to the patient and physician. The procedure is done by the fluorescent antibody technique. Table XII shows the services rendered by the Laboratories of the Department of Health to the community from samples sent from public and private hospitals and from physicians' offices. The re-

sult of the test is available to the clinician either the same day or within 24 hours in order to permit the institution of the indicated penicillin regime for the positive cases. The Department of Health provides the penicillin free of charge, for the primary prophylaxis and also for secondary prophylaxis by providing the required ampules of 1,200,000 units of benzathine penicillin for monthly use.

Summary and Conclusions

In order to obtain a clearer picture of the problem of rheumatic fever (RF) and rheumatic heart disease (RHD) in Puerto Rico a perusal of the literature and a compilation of the available unpublished data was done.

Autopsy studies have revealed that 20 percent of all cardiac deaths reported by Koppisch in 1944 were due to RHD. Three recent autopsy studies revealed that 8.4 percent, 7.7 percent and 7.9 percent of all cardiac deaths were due to rheumatic heart disease.

Francisco encountered that RHD was responsible for 25 to 30 percent of all cardiac cases admitted to Bayamón District and Arecibo District Hospital from 1939 to 1943 respectively. Clinical studies from 1946 to 1962 presented by different authors show that RHD was responsible for 10.4 percent to 19.8 percent of cardiac patients seen at clinics.

An analysis of the experience of the Heart Disease Control Program clinics for the period of July 1, 1962 to June 30, 1967 shows that of a total of 8,389 cardiac patients admitted to the clinics 1,029 (12.2 percent) were patients with RHD. There was no apparent difference in the geographical distribution of cases.

Vital statistics from the Demographic Registry have shown that in the years of 1950 to 1966 RHD has accounted for 3.05 percent of all cardiac deaths. Rheumatic heart disease constitutes the commonest cause of cardiac death in the age group of 10-30 years.

The studies carried on Group A beta-hemolytic streptococcus in Puerto Rico have been summarized. The results of the fluorescent antibody studies carried on by the Laboratories of the Department of Health is included.

Statistical information concerning other types of heart disease has been included in the tables, so that the relative importance of each type of heart disease can be assessed.

Resumen y Conclusiones

Para obtener un cuadro más claro del problema de la fiebre reumática y enfermedad reumática del corazón en Puerto Rico se ha revisado la literatura y se ha recopilado la información local accesible que existe sin publicar sobre este tema. Los estudios de autopsias revelaron que el 20 porciento de las muertes cardiovasculares informadas por Koppish en el 1944 se debían a enfermedad reumática del corazón. Tres estudios de autopsias recientes revelaron que el 8.4 porciento, 7.7 porciento y 7.9 porciento de todas las muertes cardíacas se debían a enfermedad reumática del corazón.

Francisco encontró que la enfermedad reumática del corazón era responsable del 25 al 30 porciento de todos los casos cardíacos admitidos a los hospitales de distrito de Bayamón y Arecibo respectivamente desde el 1939 al 1943. Estudios clínicos desde el 1946 al 1962 presentados por diversos autores demuestran que la enfermedad reumática del corazón fue responsable por el 10.4 porciento al 19.8 porciento de los pacientes cardíacos nuevos vistos en clínicas de corazón.

Un análisis de la experiencia de las clínicas en el Programa para Control de las Enfermedades del Corazón del Departamento de Salud durante el período del 1ro. de julio de 1962 al 30 de junio del 1967 demostró que de un total de 8,389 pacientes cardíacos admitidos a las clínicas 1,029 (12.2 porciento) eran pacientes con enfermedad reumática del corazón. No hubo una diferencia aparente en la distribución geográfica de los casos.

Las estadísticas vitales del Registro Demográfico han demostrado que en los años 1950-1966 la enfermedad reumática del corazón fue responsable por 3.05 porciento de las muertes cardiovasculares. La enfermedad reumática del corazón constituye la causa más común de muertes en el grupo de edad de 10-30 años.

Los estudios que se han hecho en Puerto Rico en relación al estreptococo grupo A beta hemolítico han sido resumidos. Se incluyen los resultados de las pruebas de anticuerpos fluorescentes realizadas por los laboratorios del Departamento de Salud. Se han incluído estadísticas sobre otros tipos de enfermedades cardíacas en las tablas de manera que se pueda captar mejor la importancia relativa de cada tipo de enfermedad cardiovascular.

Acknowledgment

We are indebted to Dr. Víctor González, Dr. Carlos Vicéns, Dr. Ramón Aixalá, Dr. A. A. Colón, Mrs. María T. Pérez, Mr. Luis A. Collazo, Mrs. Carmen Benejam, and Mrs. L. L. Danielsen from the Department of Health of the Commonwealth of Puerto Rico for their cooperation in obtaining the Heart Disease Control Program and Demographic Registry information.

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SUBLESIONAL STEROIDS IN THE TREATMENT OF CHRONIC DERMATOSES

Evaluation of a new steroid suspension

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Ever since the advent of steroids and the recognition of their marked anti-inflammatory and antipruritic actions they have become a potent therapeutic modality in skin diseases. Initially hydrocortisone and then a host of derivatives have been used topically. One of the major obstacles to this method is the relative impermeability of the epidermis, so that the medicament often fails to exert its beneficial action at the desired depth. Certain changes in the chemical composition of these drugs have increased their penetrability. This has also been achieved with the techniques of occlusive dressings with polyethylene plastic films (1, 2). The prolonged contact and the increased moisture under the occlusive film enhance the percutaneous absorption of the steroid in water miscible creams.

Evidently the most direct method of getting a steroid into a skin lesion is injecting it into or under the affected skin. This is especially desirable for chronic dermatoses characterized by thickening of the epidermis and inflammation of the dermis such as circumscribed neurodermatitis, localized patches of psoriasis (3, 4) and certain types of lichen planus, or where there is thickening of the dermal connective tissue as in keloids (5), hypertrophic scars and localized scleroderma, or in other patchy diseases such as alopecia areata (6, 7) and chronic discoid lupus erythematosus (8, 9). The oral administration of steroids has been found effective in some of these conditions but the fairly high and prolonged doses required, with their well known side effects, make this route much less favorable.

The local injection of relatively small amounts of long-acting (low solubility) steroids permits therapeutic efficacy without systemic reactions. Hydrocortisone acetate suspensions, 25-50 milligrams per milliliter, have been used for several years with satisfactory results. Suspensions of prednisolone (acetate), triamcinolone (diacetate, acetonide) and others have improved the results of hydrocortisone. A new derivative of triamcinolone, the hexacetonide, has been found to exhibit potent anti-inflammatory effects. It is less soluble in water than the diacetate, thus, its action is expected to be more prolonged when injected intralesionally. Reports of its use in chronic dermatoses are encouraging (10, 11).

A study on the comparative effects of traimcinolone acetonide and the newer hexacetonide in chronic dermatoses was carried out and is reported here.

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Material and Methods

Fifty patients, selected mostly from the Der-

matology Clinics of the University Hospital and a few from private practice, were studied from August 1966 to December 1967. Forty four of these are included in the final analysis, 6 not participating because of insufficient follow-up. The conditions treated were as follows: 18 cases of chronic lichenified dermatitis (13 of classical neurodermatitis, 3 of "psoriasiform" neurodermatitis, and 1 each of chronic dermatitis with nummular lesions and dermatitis persisting after chronic contact dermatitis of the feet), 8 cases of psoriasis, 6 of keloids and hypertrophic scars, 5 of chronic discoid lupus erythematosus, 2 of lichenoid amyloidosis, and 1 each of prurigo nodularis, localized scleroderma, lichen planus, alopecia totalis and histiocytosis X (Hand-Schuller-Christian type) with seborrheic dermatitis-like lesions. Comparative areas were injected at weekly to monthly intervals with equal amounts of aqueous suspensions of triamcinolone acetonide 10 milligrams per ml in one side and triamcinolone hexacetonide 5 milligrams per ml in the contralateral side of the body. When only one side was affected the lesion was roughly bisected and each half treated accordingly. Saline solution was also injected into a third site but it was discontinued early in the study after observing consistently negative results. Injections were made with from 0.25-1.0 ml of suspension using the ordinary disposable syringe needle method (12) and/or the dermojet, a pistol-like instrument similar to the one used for mass vaccinations, which injects in each shot 0.1 ml of suspension intradermally. In a few cases submitted to the needle technique 0.25-0.5 ml of xylocaine was added to the suspension to minimize pain. Photographs were taken initially in most cases and during follow-up visits in some. The period of observation varied from one month to one year.

Results

The results are summarized in Table I.

The injected sites in patients with chronic lichenified dermatitis and psoriasis responded very well. After two or three injections the patch became asymptomatic and flattened out, frequently showing as a valley surrounded by the active, untreated areas. The response was more or less the same with the two suspensions but it was noticed that recurrences were more apt to occur in the acetonide-injected areas. In general, patches treated with the hexacetonide were somewhat slower in response but remained asymptomatic more persistently than those treated with the acetonide.

In chronic discoid lupus erythematosus (LE) the results were equally satisfactory for the two drugs but less so than with lichenified dermatitis and psoriasis. The activity in discoid LE, as evidenced by scaling and erythema, tended to recur in the periphery of areas treated with the acetonide but not with the hexacetonide. In one case there was marked atrophy and persistence of whitish crystals in the center of a patch treated with the hexacetonide.

Keloids and hypertrophic scars generally responded better to the hexacetonide with softening and disappearance of itching and burning. In one instance the hypertrophic scars actually became depressed ("pseudo-atrophy") after two injections of hexacetonide suspension. The acetonide-injected area did not show appreciable flattening. In one case of localized scleroderma the patch became noticeably softer.

Considerable diminution to disappearance of itching was obtained in one case each of lichenoid amyloidosis, prurigo nodularis, lichen planus and the seborrheic dermatitis-like lesions of the scalp of a woman with the Hand-Schuller-Christian variety of histiocytosis X. No regrowth of hair occurred

in one patient with total alopecia of the scalp.

Various degrees of inflammatory reaction, ranging from erythema and slight edema and tenderness to abscess formation, occurred in the injected areas in three cases. This complication was controlled with standard topical and antibiotic therapy.

TABLE I : SUBLESIONAL TRIAMCINOLONE HEXACETONIDE AND TRIAMCINOLONE ACETONIDE IN CHRONIC DERMATOSES

Diagnosis	No. of Patients	Results	Comments
Lichenified dermatitis	18	Good to excellent equally with both drugs	Acetonide-treated areas relapsed in one case
Psoriasis	8	Good to excellent equally with both drugs	Acetonide-treated areas relapsed in 2 cases and in 1 in hexacetonide-treated areas
Chronic discoid lupus erythematosus	5	Moderate improvement equally with both drugs	Recurred in 3 acetonide-treated cases. Marked pseudoatrophy in one case treated with hexacetonide.
Keloids and hypertrophic scars	4	Hexacetonide better (fair to marked improvement) in 3; in 1 both equal	2 additional cases treated with hexacetonide alone got moderate to marked improvement
Lichenoid amyloidosis	2	Both equal in obtaining moderate improvement in 1, none in the other	Condition notoriously recalcitrant to any treatment
Prurigo nodularis	1	Considerable diminution of itching with both	Condition notoriously recalcitrant to any treatment
Scleroderma, localized	1	Softening of the patch with both	Condition notoriously recalcitrant to any treatment
Lichen planus	1	Moderate improvement with both	Some pseudoatrophy with both
Alopecia totalis	1	No effect from either	Condition usually recalcitrant
Histiocytosis X, scalp lesions	1	Diminution of itching with both	Rash persisted

Discussion

The use of sublesional injections of steroids is a big step forward in the treatment of chronic dermatoses. These diseases are not "cured" by this modality, since treated areas tend to recur sooner or later and certainly when the condition is generalized it is impractical to inject all sites, but in annoying circumscribed or disfiguring patches the results are superior and more long-lasting than with other available therapy. A patch of itchy neurodermatitis, or an ugly and burning keloid or hypertrophic scar, or a group of disgusting psoriatic lesions may be made to involute or actually disappear for prolonged periods of time.

The complications of this therapy are minimal and controllable. Such events as amaurosis after infection of alopecia areata (13) are extremely rare. Local reactions are uncommon (less than 0.5 percent) and systemic reactions rare (less than 0.1 percent) (14). The most commonly observed undesirable effects are: (1) pain and discomfort, which are minimized by adding xylocaine to the suspension, (2) secondary infections, amenable to standard therapy and preventable in the great majority of cases by adequate antiseptic technique, and (3) atrophy, which is really pseudoatrophy because the skin reverts to its normal state later on.

It may seem unreasonable to attempt a comparison between locally injected drugs, especially when the proximity of the areas permits diffusion of the drug to the vicinity. However, these steroid suspensions, being slightly soluble, remain fairly well localized to the injected site, sometimes persisting there for long periods as evidenced by the presence of their whitish crystals many months later. It is also observed more often than not that the beneficial action is limited to the confines of the injection, the uninjected neighboring area staying unaltered in its activity. Thus, it is possible to attempt a comparison between two drugs in these circumstances. Certainly, when injections are given in contralateral areas, the comparison is quite fair.

In this study it was found that both triamcinolone hexacetonide and the acetonide are equally effective in controlling pruritus and levelling the lesions of chronic lichenified dermatitis and psoriasis, and in disappearing the erythema and scaling of discoid lupus erythematosus. It is apparent, at least in some instances, that although the beneficial action of the acetonide precedes that of the hexacetonide, the latter persists for a longer period of time, probably based on its lesser solubility. This was nicely illustrated in one case of chronic discoid lupus erythematosus, a disease which is atrophic per se, in which the hexacetonide–injected patches became quite depressed and showed deposited crystals, almost a year after injections, whereas the acetonide-injected areas showed peripheral recurrence of activity at that time.

Although no regrowth of hair occurred in one case of alopecia totalis it is well known that alopecia areata responds to this modality. Total or universal alopecia, which may be regarded as a "malignant" generalization of alopecia areata, is notoriously stubborn to treatment. Regrowth of hair may occur with steroids but it is usually patchy and temporary.

It is conforting to find that at least one case of lichenoid amyloidosis and one of prurigo nodularis, both bêtes noires in dermatological therapy, obtained fairly satisfactory results with this approach.

Summary

The intra- or sublesional injection of aqueous suspensions of certain low-solubility steroids is beneficial in the treatment of various chronic skin diseases. This is a welcome modality in the dermatological armamentarium since most of these diseases are known for their stubbornness in responding to previous therapy. Localized patches of neurodermatitis, psoriasis, chronic discoid lupus erythematosus, and lichen planus respond satisfactorily, although recurrences do occur. However, these new patches may be reinjected and further remissions obtained. Keloids and hypertrophic scars can be softened and flattened. Hair may be regrown in alopecia areata but alopecia totalis usually remains unchanged or responds only temporarily. Improvement may also be obtained in rarer diseases such as lichenoid amyloidosis and prurigo nodularis, formerly impassive to therapy.

A suspension of 5 milligrams per ml of triamcinolone hexacetonide was found to have a similar beneficial effect to that obtained with one of 10 milligrams per ml of triamcinolone acetonide, except in keloids and hypertrophic scars where the hexacetonide was superior. The good results following the use of the hexacetonide were found to be more persistent than with the acetonide suspension.

Resumen

La inyección intra- o sublesional de suspensiones acuosas de ciertos esteroides de baja solubilidad es beneficiosa en algunas dermatosis crónicas. Esto representa una valiosa adición a la terapéutica dermatológica ya que la mayoría de estas enfermedades son recalcitrantes a los métodos tradicionales. Placas circunscritas de neurodermatitis, psoriasis, lupus eritematoso discoide crónico, y liquen plano, responden satisfactoriamente, aunque suelen haber recurrencias. Sin embargo, se pueden lograr nuevas remisiones al reinyectar las lesiones reactivadas. Los queloides y las cicatrices hipertróficas se ablandan y aplanan. Se logra el crecimiento del pelo en alopecia areata pero alopecia totalis generalmente no responde o sólo se logra un crecimiento temporero. Se puede obtener alguna mejoría en enfermedades más raras como liquen amiloidoso y prurigo nodular, previamente intocables.

Se encontró que una suspensión de 5 miligramos por ml de la hexacetonida de triamcinolona tuvo un efecto beneficioso comparable al de una de 10 miligramos por ml de la acetonida de este mismo esteroide, excepto en queloides y cicatrices hipertróficas en las cuales la hexacetonida resultó ser superior. Los buenos resultados son más persistentes con la hexacetonida.

The triamcinolone hexacetonide (Aristospan ®, 5 milligrams per ml was supplied by the American Cyanamid Company, Lederle branch. The triamcinolone acetonide suspension, 10 milligrams per ml, utilized, was Kenalog ®, parenteral (Squibb).

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BEYOND THE UNCONSCIOUS: THE ULTRACONSCIOUS *

Stanley R. Dean, MD

"Never throw away hastily any old faith, tradition or convention. They may require modification, but they are the result of the experience of many generations."

Sir Oliver Lodge

We are about to enter the rarefied atmosphere of an esoteric realm, hitherto pre-empted chiefly by religion, philosophy and mysticism.

But I see no reason why an ordinary psychiatrist like myself, who is no pedagog nor member of an elite group, should hesitate to approach its threshold, examine its terrain, point out areas of interest and, hopefully, encourage others to explore more thoroughly.

I refer to a supra-sensory, supra-rational region of the mind, whose existence has been known since antiquity. It is figuratively as remote from the conscious and the unconscious mind as outer space is from the earth and moon. It is related to, if not identical with, the nirvana of Buddhism; satori of Zen; samadhi of Yoga; Bucke's "cosmic consciousness:" and existentialism's "kairos."

**The prefix, "Ultra," is used here in the dictionary sense of "beyond, ultimate, extraordinary." In discussing this subject with many persons, both lay and professional, I have found that the term, "Ultraconscious," seems to "reach" them better than any other; i.e., "Ultraconscious" seems to have clearer semantic validity. Also, the word, "Ultraconscious," is more naturally coupled with Freud's, "Unconscious," yet conveys the meaning of beyond the Unconscious."*

Miraculous powers have been attributed to it, and from it had sprung the highest creativity and genius known to man. Yet it has received surprisingly little attention from modern science, and still remains one of the greatest enigmas of the mind.

For the sake of uniformity I shall refer to it as "Ultraconsciousness," and I shall express the hope that in an age in which Man has finally embarked upon a systematic exploration of the outer reaches of Space, he shall at long last embark upon an equally systematic exploration of the outer reaches of the Mind, even though it takes him far beyond the Unconscious that Freud's intrepid pioneering has established as a relay station.

There is a facetious saying that Psychiatry has developed so amazingly in recent years that it is now almost impossible to find a normal person.

Yet the secret of mental health still remains a secret!

Is it not possible that in our headlong quest for new answers, we may be overlooking some old ones? As science annihilates space and accelerates communication between the modern culture of the West and the ancient culture of the East, that possibility recurs with increasing frequency. That is as it should be. Today East and West enjoy a transcultural relationship unique in world history, and full of promise for a vast expansion of our knowledge of human behavior.

It provides us with an unequalled opportunity to re-discover ideas which, if too long hidden, might be lost.

Let us examine some of them. In so doing I make no claim of originality, but have borrowed freely from many sources, some directly and others indirectly. I am especially indebted to the inspiring erudition of Dr. Harold Kelman, Dr. David Shakow and Dr. William Caudill in the United States; and to Dr. Koji Sato, Dr. Akira Kasamatsu and Zen-Master Ishiguro in Japan.

My purpose in this presentation is to epitomize, dramatize and, perchance, catalyze what others have stated much better than I can hope to do. It may even be an advantage that I am not overburdened by too much knowledge, for my subject is somewhat like a baby--easy to conceive but hard to deliver--so that I have reason to be vehemently simple--and brief.

To begin with, Western psychiatry has concerned itself chiefly with psychology and physiology, but scarcely at all with Eastern spirituality. Yet the latter is trying desperately to catch up with and integrate with the scientific-material-objective progress of the West. The two should not remain mutually exclusive. The time is ripe for large-scale integration, and we should meet if half-way, if for no other reason than the very practical one that healing factors are intrinsic in Eastern spirituality that might well enrich our current psychotherapeutic armamentarium. As practicioners of the healing arts, we simply cannot afford to dismiss any therapeutic procedure that holds potential promise.

No psychiatrist should look down on what he is not up on!

Man has always been fascinated with the world of the spirit. There is a natural tendency for the uncluttered mind to drift towards the abstract, and we need not fear that science will be compromised by it, for many scientific facts began as abstract theories. It is even intriguing to speculate that as computer machines take over more and more of the chores of calculation and conceptualization, Man's liberated mind may again resume its age-old contemplation of the enigma of the spirit.

Let us proceed to a clarification of terms. In the sense used here, Eastern spirituality refers to an extraordinary state of mental immobilization that literally transcends reason. It has many levels, but its ultimate manifestation--when the mind becomes dismantled of all objective form and content--is a state of consciousness far more pure and fundamental and absolute than ordinary consciousness or even unconsciousness. Haas has described it as "an awareness without anything of which awareness is aware." Offhand, that may sound like something written by Gertrude Stein, but it is, nevertheless, a sincere, if admittedly groping attempt to describe what many regard as indescribable. However, we shall not let ourselves become discouraged by the limitations of language, but shall with unabashed confidence trust intuition to augument mere words; for, as Thomas Huxley stated: "A world of facts lies outside and beyond the world of words."

The Ultraconscious mind at its summit, is characterized by a state of cognitive suspension that Zen refers to as "no-thought" or "no-mind." Incredibly, however,--and this is the very essence of my report--when the mind ceases to think, it does not cease to be--for now an extraordinary phenomenon emerges: a form of mentation so profound that thaumaturgic properties have been ascribed to it; so enobling that men have abandoned material wealth for it; so supercharged with creativity that the course of history has been influenced by it.

Although, as stated before, it has been considered indescribable, many attempts have been

made to describe it through such limited terms as: illumination, intuitive insight, ineffable grace, transcendant lucidity, sublimity, Godliness, *unio mystice*, *summum bonum*, etc. At times it may be accompanied by a sensation of dazzling radiance--perhaps the progenitor of our everyday expression, "to see the light." But perhaps the feature that has most affected the imagination and destiny of the initiate is the overwhelming, intuitive awareness of a supreme and infinite Being--an experience that is too stupendous to remain self-contained, and may create an irrestable impulse to inspire others. Is that what motivated Abraham, Moses, Buddha, Christ, St. Paul and Mohammed? Does it prove that there really is a God, Creator, Supreme Being? Or is it that Creator actually a projection of the immortal creativity of man, himself? In brief, did God create man--or did Man create God? These questions have been asked throughout the ages, and I raise them here for philosophical interest, and not because I am intellectually or morally equipped to answer them.

Let us return to a more immediate examination of the ultraconscious. To those who conversant with it, Ultraconsciousness reprcsents the Real rather than Reality; Wisdom rather than Knowledge. Kelman points out that knowledge demands answers to its questions of why, who, where, when, what and how. Wisdom, however, according to Zen, is the essence of "no-answers": forms and phenomena are dismantled of their contents, diffused rather than concretized, experienced rather than explained, and dispersed rather than unified. Whereas the West desires, the East seeks desirelessness.

Eastern cognition is interested in pure consciousness itself. Western cognition is interested in subject-object relationships of consciousness. Therefore, the Western mind rebels at being carried to its ultimate state of absolute consciousness because the object would disappear and there would be pure subject. The Eastern mind is concerned, however, with intuition as pure and absolute subjectivity, pure disembodied consciousness.

Stated another way, The West is concerned with finding ways and means of ascertaining reality through logic (logos) that will brush aside doubt and criticism. The East has made pure consciousness itself the object of its interest, and in this ultimate quest, has dismantled phenomena of their object-content. The one uses a doctrine of words, the other accepts a wordless doctrine.

I agree with Kelman that Freud, through his concepts of free-association and the unconscious, dared to challenge the supremacy of Reason, and, unintentionally, set in motion a rcunion of Western man with the East. But long before Freud, the Oricnt made that challenge and went far beyond the concept of the unconscious in their discovery of absolute consciousness. Free-association could be a step in that direction if used as pure catharsis rather than for the purpose of object interpretation. In freer and freer association, Kelman affirms, it is not enough for the forms, the objects, the phenomena to emerge; they must continue until they are resorbed, attachment to them diminishes, and they entirely disappear--until there is complete formlessncss, intuitive insight, supra-sensory lucidity and ultimately nirvana (satori).

It would be a fertile subject for research to determine to what extent Freud's theory actually was influenced by Eastern spirituality. It stands to reason that a man who could write, "Moses and Monotheism" and "Totem and Taboo," must have had an intimate knowledge of Eastern spirituality. But would he admit it or credit it? We know how anxious he was to find favor with his scientific colleagues for he was himself a trained scientist, and he tried, as did his followers,

to invest his theories with a scientific aura. At one point he even said, "All that is outside of science is delusion, particularly religion." But we may well question if his heart was really in it. For, in "Moses and Monotheism," while discussing the abolition of idols by the Jews, he makes this remarkably revealing observation: "It was bound to exercise a profound influence. For it signified subordinating sense perception to an idea; *it was a triumph of spirituality over the senses.*" Was that statement indeed a personal confession disguised in projected form? If so, it could throw new light on Freud's ultimate thinking, and encourage his followers to expand his frontiers with confidence.

The goal of ultraconsciousness can become increasingly possible to the Westerner as we learn more about Eastern techniques. When the West relinquishes its over-dependency on scientific-objective-logical-realism and makes the leap into the nonconceptual realm of pure, intuitive consciousness, we can then start moving towards a new synthesis of East and West--towards a spirituality which, when added to our psycho-physiological knowledge, may well contribute to a more congruent wholeness--to a more vastly expanded psychotherapy.

Implicit, of course, in Kelman's thesis which I have just outlined, is a plea for the return of the guru-chela (master-disciple) relationship of the East, a trend that has already gained such momentum from Freud. Others, following Freud's example, have also moved us closer to the East: specifically, Jung's collective unconscious; Fromm's and Horney's emphasis on moral values; and the existential doctrine that there is no difference between the external world and the internal world of the mind.

I have so far discussed some of the general background of the Ultraconscious mind. Now I should like to stress a property of particular interest to the physician and psychiatrist: that is, its ability to produce freedom from physical and mental pain. That quality alone should constitute an incentive for us to understand and utilize it. Faith healers are aware of it, and all of us have probably encountered it in some form. It may occur spontaneously, especially under conditions of stress, but as a rule, has necessitated long periods of dedication, contemplation and intense physical and mental discipline. It undoubtedly plays some part in group therapy such as Alcoholics Anonymous. I remember once hearing this testimonial from a former alcoholic:

> "After being semi--conscious for more than a week, I opened my eyes one morning and looked up--and there I saw the gutter. But I looked higher and saw the sky and it was aglow with a heavenly light. And at that instant something wonderful happened to me. I knew with absolute conviction that I was cured, that I would never drink again and would be a better man than I had ever been before! "

That was his satori, his Kairos, his cosmic consciousness. It had occurred twenty years before, and since that time--without a word of psychotherapy as we know it--he has been not only cured of his alcoholism, but has been a man in word and deed far transported above his former self.

Kelman--expanding the theories of Kielholz and Ellenberger--believes that major and minor periods of illumination (which he calls "kairo") could be *helped* to happen in patients, could be recognized when they did happen, and could be used by psychiatrists to augument present psychotherapy.

My own interest in the subject occurred as the result of a chance encounter with Zen during one of my visits to Japan. Two colleagues, Dr. Sato, professor of psychology at Kyoto University and Dr. Kasamatsu, professor of neuropsychiatry at Koishigawa Hospital

of Tokyo University, arranged for me to take motion-pictures at the institute of Zen-Master Horyu Ishigurb in Tokyo--and, in so doing I later learned that I inadvertently was the first American to make a film of the Zen ritual. At the time my interest was purely that of an observer and reporter; but somewhere along the way I was pricked by the thorn of knowledge--was it "Kairos? "--and as a result have become more and more dedicated to the proposition that Psychiatry should, at long last, embark upon a serious and systematic investigation of this omnipresent phenomenon. Such a study may well provide a missing link in the expanding chain of psychotherapy, at the very least it should add another dimension to our understanding of the manifold wonders of the mind.

Japan, of course, has a bit of a head start, for Zen is about 12 centuries old. It had however, degenerated into aristocrat intellectualism until new life was injected into Zen by the introduction of the Koan exercise some 800 years ago.

A Koan is a statement by a Zen master or an answer given to a questioner. From the viewpoint of empirical consciousness, and sense impression these Koans seem completely illogical, unconventional and incomprehensible. Examples might be: How do you clap your hands if you have only one hand? Or, where would you rather be, in the country or in the summertime?

They express paradoxes, contradictions, affirmations, negations and exclamations. These function to bring about a highly wrought-up state of consciousness and frustration. The reasoning faculty is kept in abeyance so that the more central and profounder parts of the mind, generally deeply buried, can be brought out. "The affective and conative centers are charged to do the utmost in the solution of problem." Finally a neutral state of consciousness, the highest peak of mental integration occurs and the empirical consciousness with its conscious and unconscious becomes relegated to the Beyond. There is a "throwing oneself down the precipice," or a "letting go the hold." At last, says Suzuki, "all psychic faculties become charged with new energies hitherto undreamed of. A penetrating insight is born on the inner depths of conscious, as the new source of life is tapped, and with it the koan yields up its secret. This realization is called "Satori."

In his "Zen Doctrine of No-Mind," Suzuki continues: "So long as there are conscious strivings to accomplish a task, the very consciousness works against it, and no task is accomplished. It is only when all traces of consciousness are wiped out that Buddhahood is attained.... The idea is that when every effort is put forward to achieve a task, and you are finally exhausted and have come to the end of energy, you give yourself up so far as your consciousness is concerned. In fact, however, your unconscious mind is still intensely bent on the work and before you realize it you find the work accomplished. This is what is meant by "to accomplish the task by no-mind..." Philosophically speaking, therefore, no special conscious strivings are necessary; in fact, they are a hindrance to the attainment of Buddahood. We are already Buddhas. To talk about any sort of attainment is a desecration, and logically a tautology.

What significance does all this have for the physician, the healer, the psychiatrist? It may mean that if investigation corroborates the importance of the Ultraconscious state, the psychiatrist may have to relearn the difficult role of philosopher physician as well as scientist-physician. Such investigation is already well under way in Japan. Kasamatsu and his associates have made numerous phy-

siological studies of the *satori* state. Sato has done much to define and analyze the psychological aspects. And Zen-Master Horyu Ishiguro, a sage in 70's, has streamlined the ritual of Zen to a point where concentrated application of his physical and mental exercises can often achieve *satori* within 5 days!

I must tell you something about this remarkable man. Master Ishiguro, now president of the Zenrigaku Society, entered into Zen more than 50 years ago, but eventually became impatient with the traditional, time-consuming methods which were concerned more with precision of manner and form than with inner problems. He retained the essential principles of Zen, i.e., the teaching of students to be in *munen-muso* (no-thought and no-feeling), to be completely in *mu* (nothing), to sit quietly and to be in *koanzammai* (absorbed in Zen questions).

But, in 1957, he developed a greatly simplified program that he has since used with great success both in teaching and therapy, and with Europeans and Americans as well as Orientals. His objective is clearly stated in his manual:

"Everybody wishes to become free from his inner pains. These pains arise because he feels them or thinks them. Therefore, it stands to reason that if he neither feels nor thinks anything at all, he will get no pains. From morning till night everyone lets his mind wander from one thing to another and keeps feeling different sensations. Thus, he presumes that the mind has to be used in the wandering state. Shakamuni (Gautama) Buddha succeeded in finding a method of using the mind in the immobile state, which is the (essence) of Zen, and by thus freeing the mind arrived at *satori* ("the great satisfaction.") Therefore, anyone who wishes to achieve satori, must succeed in the method of using the mind in the immobile state as did Shakamuni Buddha."

EDITORIALES

HERNIA HIATAL

Por muchos años el esófago fue considerado como órgano de poca importancia en el sistema digestivo. Se ha acusado a los gastroenterólogos de no incluírsele en el nombre de la especialidad. Hasta muy recientemente la radiología contribuyó muy poco al estudio de la fisiología y la fisiopatología del esófago debido, en parte, a que los estudios radioscópicos casi siempre se hacían en bipedestación y por otra parte, a que los aparatos usados en radiología no eran lo suficientemente potentes para poder hacer una investigación prolífica del esófago en general y muy especialmente del esófago terminal.

Por estas razones las hernias gastro-esofágicas no eran diagnosticadas. Con los nuevos métodos de investigación radiológica se han llevado a cabo estudios exhaustivos de la fisiología del esófago pero, a pesar de todos los recursos hoy disponibles, todavía hay una gran incertidumbre sobre cuál es la verdadera anatomía y fisiología del tercio distal del esófago. Debido a estas dificultades los fisiólogos han estudiado extensamente por métodos manométricos todo el esófago y muy especialmente, la región del esófago abdominal pero, al igual que con la radiología, se ha hecho muy difícil el establecer conceptos que sean aceptados por todos los investigadores. Hasta hace poco se consideraba por los expertos en manometría esofágica que el punto de la inversión de la presión (PIP) positiva a negativa, al retirarse la sonda del estómago hacia el esófago, indicaba la posición anatómica del hiatus diafragmático. Los estudios de otros investigadores han demostrado hasta dónde se puede decir categóricamente que esta interpretación no es correcta y que por el contrario el PIP representa el esfincter del cardias esofágico que separa el esófago del resto del trayecto gastrointestinal.

El Dr. Lazlo Ehrlich en este número nos demuestra, con lujo de detalles, las dificultades con que se confrontan los que se dedican a los aspectos radiológicos del cardias esofágico y, tras investigaciones llevadas a cabo, concluye que el problema principal en la radiología esofágica es la demostración del reflujo gastroesofágico y no propiamente la presencia de la hernia gastroesofágica a través del hiatus diafragmático.

Todos hemos visto innumerables personas que tienen "hernia hiatal" sin o con

muy pocos síntomas, no importa el tamaño de la hernia, reflujos asintomáticos y asimismo hemos visto pacientes con sintomatología gastroesofágica pronunciada sin que se pueda demostrar anormalidad alguna con el examen radiológico rutinario. El Dr. Ehrlich demuestra que es necesario el utilizar una técnica radiográfica especial para encontrar el "crux" del problema y no hay duda alguna que así lo es de acuerdo a las excelentes radiografías presentadas. Me parece sin embargo que muy pocos seres humanos se dedican a tomar líquidos en la posición horizontal y por lo tanto lo más importante para el enfermo con trastornos gastroesofágicos es que no lo haga, que evite el aumento de la presión intra-abdominal, que baje de peso, que no se acueste boca abajo, que no se apriete la barriga, que se acueste con el estómago vacío y nunca en posición ventro-horizontal y que siga un régimen dietético y medicamentoso adecuado.

F. Hernández-Morales, MD, FACP

A NEW FEATURE: QUESTIONS AND ANSWERS

It has been the desire of the editorial board to make the Boletín not only an outlet for scientific publications for our medical colleagues here in Puerto Rico. but also to be a medium for sharing common medical problems.

There are undoubtedly many problems that come up in our every day practice which we would like to discuss with others and seek to benefit from the experiences of other physicians who have faced similar problems. The Boletín is therefore planning to devote a section for questions and answers.

Questions sent by physicians will be referred for answers to those who are considered best qualified in the particular field in question. The querying physician will receive an early personal reply by return mail. while in the monthly Boletín. all questions with the answers considered to be of general interest and benefit will be published in the special section. (The name of the physician sending the question will be omitted unless otherwise specified by the physician.)

This is an educational venture and its success will depend on the active participation of all of us.

Nathan Rifkinson. M. D.

ACTUALIDADES MEDICAS

Automated Multiphasic Screening

Dramatically more effective detection, prevention and control of chronic disease and disability has been made possible through automated multiphasic screening procedures, according to information reported at the 53rd annual meeting of thc Industrial Medical Association being held this week at the San Francisco Hilton.

Morris F. Collen, M.D., Director of Medical Methods Research for the Permanente Medical Group, Oakland, Calif., said that the computer storage of data on more than 40,000 adults annually in their laboratories permits extensive epidemiological research, especially directed towards the preventive aspects of chronic disease.

The automated laboratory portion of the routine periodic health examination includes the electrocardiogram, chest x-ray, breast x-ray in women 48 and over, body measurements, pulse and blood pressure, visual acuity, ocular tension, retinal photograph, forced expiratory vital capacity, pain reaction test, hearing test, self-administered health questionnaire, tetanus toxoid immunization, blood chemistries, blood hemoglobin and white cell count, blood group, serological test for syphilis, blood rheumatoid factor and urinalysis. Additional tests are arranged by means of a computer in accordance with programmed "advice" rules, based upon normal limits for test values generated from the population studied.

Dr. Collen explained that if a patient's summary report printout indicates certain combinations of symptoms and test values which fulfill the criteria for selected diagnostic categories, it is suggested that the physician consider these diagnoses. The physician reviews the summary report at the time of the patient's office visits, directs further history toward elaborating upon the questions to which the patient has answered "yes," and to the reported test abnormalities. He completes his physical examination and communicates back to the computer by recording his findings and the patient's final diagnoses on a form which is processed through an optical reader and stored in the computer.

Speaking at the same session, Thomas B. Weber, Ph.D., President of Bioscience Planning, Inc., Anaheim, Calif., said that it appears that the present state-of-the-art in multiphasic screening has reached the point where it will prove economically feasible for industry to consider the development of periodic health examinations for their employees. He referred to studies performed on the cost-effectiveness of periodic health examinations in the industrial setting which have shown satisfying employee health and medical care cost reductions.

An extensive six-month study has identified 45 such protocols that are presently in operation in the United States and Canada, according to Dr. Weber, who added that past experience suggests that the mobile unit concept can effectively meet the requirements of those companies where the number of the location of employees does not permit in-plant medical and health services.

NOTICIAS

Locales

Agosto 16: 7:00 PM - AMPR - Graduación Clase Graduandos Enfermeras Hospital Presbiteriano.

Agosto 26: 8:00 PM - Coctel Western Hemisphere Nutrition Congress II - AMPR.

Agosto 26-29: Western Hemisphere Nutrition Congress II - San Jerónimo Hilton.

Septiembre 1 - Día del Médico.

Septiembre 21 - 8:00 PM - Homenaje Dr. Fernando Cabrera - Hotel San Juan - Salón Isla Verde.

Septiembre 10-11 - AMA Speakers Program Seminar in cooperation with Puerto Rico Medical Association - Hotel Puerto Rico Sheraton.

Nacionales

NEUROLOGISTS AND NEUROSURGEONS TO HOLD JOINT WORLD CONGRESSES

The Ninth International Congress of Neurology and the Fourth International Congress of Neurological Surgery will be held as a combined scientific meeting in New York City, Sept. 20-27, 1969. This first joint meeting of the two groups will be called the World Congresses of Neurological Sciences.

ASOCIACION AUSPICIA NUEVO PROGRAMA COMPRENSIVO DE SEGUROS DE GRUPO.

ESTARA DISPONIBLE PARA MIEMBROS Y FAMILIARES EN O ALREDEDOR DE NOVIEMBRE 15

Después de casi 2 años de estudios y trabajo, la Asociación Médica de Puerto Rico, a través de la Junta de Directores, oficialmente ha aprobado y endosado un programa completo de *seguros de accidentes, salud y vida* para toda la matrícula.

De acuerdo con el programa aprobado, que se considera no tiene igual tanto en calidad como en economía, los miembros podrán *economizarse de un 50 a un 60 porciento* en estos tipos de seguro, aparte de que las reclamaciones serán atendidas localmente, aquí mismo en Puerto Rico, y de que con el logro de una muy modesta participación la emisión de los seguros será garantizada, sin importar el estado de salud del solicitante.

El Programa -- que consiste de protección de ingresos por incapacidad, plan médico mayor de $10,000 y seguro de vida -- también estará disponible para su familia, asi como sus empleados y los familiares de estos.

Pronto se enviarán a todos los miembros que estén al día en sus cuotas (esto es requisito para ser elegible) detalles completos y blancos de solicitud, aparte de que se seguirá informando a través de las páginas de este Boletín. Esté pendiente de ellas.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

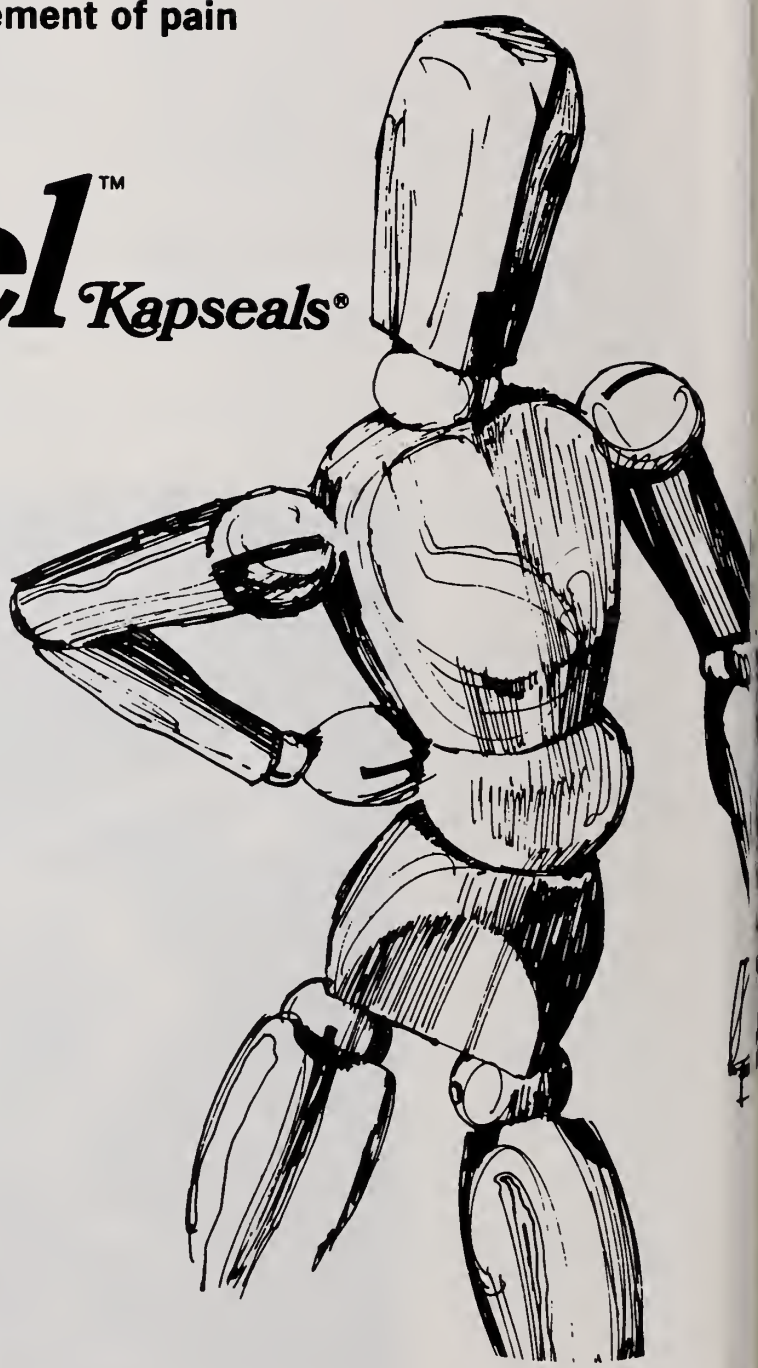
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Warning: If renal impairment exists, even usual doses may lead to liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. Hypersensitive individuals may develop a photodynamic reaction to natural or artificial sunlight during use. Individuals with a history of photosensitivity reactions should avoid direct exposure while under treatment, which should be discontinued at first evidence of skin discomfort.

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Adverse Reactions: Gastrointestinal—anore nausea, vomiting, diarrhea, stomatitis, gloss enterocolitis, pruritus ani. Skin—maculopap and erythematous rashes (a case of exfolia dermatitis has been reported); photosensitiv onycholysis and discoloration of nails (ra Kidney—rise in BUN, apparently dose rela Hypersensitivity reactions—urticaria, angior rotic edema, anaphylaxis. In young infa bulging fontanels following full therape dosage has been reported. This has disappea rapidly when drug was discontinued. Tee dental staining (yellow-brown) in children mothers given tetracycline during the la half of pregnancy and in children given drug during the neonatal period, infancy, early childhood. Enamel hypoplasia has b seen in a few children. Blood—anemia, thr bocytopenic purpura, neutropenia, eosinoph Liver—cholestasis (rare), usually at high dos If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

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at less cost to the patient than other major PVD agents

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Side Effect: Occasional palpitation.
Precautions: Use with caution in the presence of a recent myocardial lesion, paroxysmal tachycardia, severe angina pectoris, thyrotoxicosis.
Contraindication: Acute myocardial infarction.
Supplied: Tablets, 6 mg., scored; bottles of 100 and 1000. Parenteral, 5 mg. per cc., 1 cc. ampuls (5 per box); 10 cc. multiple-dose vials (1 per box).
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Whenever anxiety induces or intensifies clinical symptoms

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(chlordiazepoxide HCl)

Quickly relieves anxiety~Helps improve response in psychophysiologic disorders~Seldom impairs mental acuity or physical coordination,on proper dosage~Has wide margin of safety

Before prescribing, please consult complete product information, a summary of which follows:.

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible i nost instances by proper dosage adjustmen out a also occasionally observed at the lowe osag ranges. In a few instances syncope has en reported. Also encountered are isolate in- stances of skin eruptions, edema, min men- strual irregularities, nausea and const tion, extrapyramidal symptoms, increased l de- creased libido—all infrequent and ger ally controlled with dosage reduction; cha es in EEG patterns (low-voltage fast activi may appear during and after treatment; bl d dys- crasias (including agranulocytosis), ja ndice and hepatic dysfunction have been re rted occasionally, making periodic blood nts and liver function tests advisable dur pro- tracted therapy.

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BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

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29 NOV 1968
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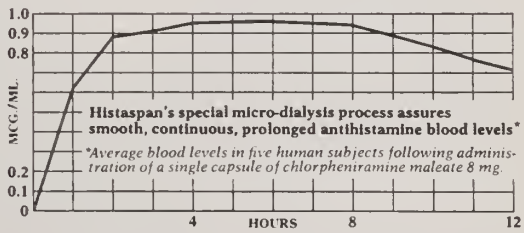
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Histaspan protects in the early morning. Pollinosis symptoms are often worst in the hours right after sunrise when seed plants discharge their pollens. Taken at bedtime, Histaspan gives allergic patients a good chance for undisturbed sleep and a symptom-free awakening. The reason: Unique among antihistamines, Histaspan provides the proven antiallergic action of chlorpheniramine in micro-dialysis cells for smooth, continuous release of medication through the night and into early morning.

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Indications: *For symptomatic relief of allergic manifestations in vasomotor rhinitis, hay fever, urticaria, angioneurotic edema, sensitivity reactions, insect bites, other itching skin conditions including pruritus ani, pruritus vulvae, pruritus of drug rashes, atopic dermatitis and contact dermatitis.* **Contraindication:** *Known hypersensitivity to the drug.* **Precautions:** *Since drowsiness or dizziness may occur, patients should be cautioned about driving or operating machinery.* **Side Effects:** *May include drowsiness, dizziness, dry mouth, disturbed coordination, blurred vision, G.I. disturbance, tachycardia, headache, nervousness, weakness, and urinary disturbances.* **Dosage:** *For both the 8 mg. and 12 mg. strengths: adults and children over age 12, one capsule in the morning, and one at night (q. 12 h.).* **How Supplied:** *Capsules—two strengths: 8 mg. and 12 mg. chlorpheniramine maleate; bottles of 100.*

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Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.
Warning: Tandearil is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.
Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.
Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reacti-

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va a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis) or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and lacuor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity, angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

For complete details, please see full Prescribing Information.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily. In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and other factors influencing drug response. Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

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Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

BOLETIN

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Anuncios y Suscripciones:

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After discontinuance of therapy, effective antibacterial levels of Vibramycin are usually present for 24-36 hours.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys

Indications: Vibramycin has been found to be clinically effective in the treatment of a variety of bacterial infections of the respiratory and genitourinary tracts and soft-tissue infections. Since Vibramycin is a member of the tetracycline series, it ma expected to be useful in the treatment of gastrointestinal, ophthalmic and other miscellaneous infections when caused by susceptible organisms.

Contraindications: Vibramycin is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: In patients with impaired renal function, reduce usual oral dosage and consider serum level determinations to avoid liver damage from excessive systemic accumulation.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although *in vitro* it binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving tetracyclines, which effect disappears rapidly on cessation of therapy.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, pruritis onycholysis and discoloration of the nails may rarely occur during tetracycline therapy, as with other antibiotics. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./da The maintenance dose may be administered as a single dose, or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infection of the urinary tract), 100 mg. every 12 hours is recommended.

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections, up to 2 mg./lb. of body weight may be used. For children over 100 lbs., the usual adult dose should be used Therapy should be continued beyond the time that symptoms and fever have subsided It should be noted, however, that effective antibacterial levels are usually present for 24 to 36 hours following the discontinuation of Vibramycin.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Aluminum hydroxide gel given with tetracycline antibiotics has been shown to decrease their absorption.

Supply: Vibramycin Hyclate (doxycyline hyclate) is available as capsules containing doxycycline hyclate equivolent to 50 mg. of doxycycline, bottles of 50.

Vibramycin Monohydrate (doxycycline monohydrate) is available as a dry powder for oral suspension containing when reconstituted doxycycline monohydrate equivalent to 25 mg. of doxycycline per 5 cc. (each teaspoonful), with a pleasant-tasting raspberry flavor, 2 oz. bottles.

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ORGANIZATION AND EXPERIENCE IN A CORONARY CARE UNIT

A Panel Discussion

Ernesto J. Marchand, MD
Luis A. Román, MD
Luis G. Borrego, MD
Clyde D. Schoenfeld, MD

Dr. Marchand:* Mr. President, members of the Puerto Rico Medical Association and guests:

"We have to tackle old problems with new ideas". This was former President John F. Kennedy's thought in the face of adversities. It happened when investigators in the United States were being concerned about more than one half million people dying every year from acute myocardial infarction despite the technical revolution including cardiac massage, defibrillation and resuscitation measures. At least 30 percent of patients hospitalized with acute heart attacks continued succumbing to their illness. Nearly one half of the deaths were considered arrhythmic in origin. This situation led Dr. Hughes Day to take the next logical step, the creation, five years ago, of the first coronary care unit with emphasis on prevention of potentially catastrophic complications.

This panel takes pride in reporting its preliminary observations of the coronary care unit of the San Juan City Hospital, the first such unit in Latin America to report its findings. We shall certainly attempt to make this panel a useful educational experience to justify your attendance.

Presented by the Department of Medicine, San Juan Municipal Hospital of the Puerto Rico Medical Center at the Annual Convention of the Puerto Rico Medical Association - November 16, 1967.

** - Chief, Medical Service.*

*Dr. Román**:* Thank you, Dr. Marchand. Members of the Association and guests: As a sequelae to the great interest developed in cardiac resuscitation in the late 50's, units for the intensive care of the coronary patient were established. Two great leaders in the field, Dr. Lawrence E. Meltzer from Philadelphia, and Dr. Hughes W. Day, from Kansas, were the first in establishing such units in 1962 (1). Their motivations were different. Dr. Day's idea surged from his interest in cardiac resuscitation (2), and Dr. Meltzer's in the prevention of arrhythmia in the coronary patient (3). Both had a common purpose in mind: to decrease the number of deaths in patients with acute myocardial infarction.

Upon reviewing the records of 760 patients dying of acute myocardial infarction, Kitchell and Meltzer found that the cause of death in 47 percent of the patients was cardiac arrhythmias (4). It had been assumed that most patients died of congestive heart failure or shock. With this concept, then, it occurred to them, that at least theoretically, 47 percent, or nearly one half of patients dying from acute myocardial infarction could be saved, if the arrhythmia was detected and treated early. That would mean the saving of hundreds of lives a year. It is said that about 500,000 patients die every year from acute myocardial infarction in the United States (3). About triple that number develop new infarcts

*** - Attending in Medicine*

every year. In Puerto Rico, with a population of 2,570,000 inhabitants 18,471 deaths occurring from July, 1964 to July, 1965 were reported. Of these 3,355 were caused by cardiovascular diseases. Acute coronary thrombosis was responsible for 1,677 deaths (59 percent) of the cardiovascular deaths. It is our impression that the mechanisms of death are the same as in the United States.

The coronary care unit at the San Juan City Hospital was officially opened in February, 1966. The idea developed in 1962 when the reports of similar units in the United States first appeared. By that time plans for the new Municipal Hospital were in progress. Provisions for an intensive care unit had been made, and so, in a sense, it was rather easy to locate physically the coronary care unit. It was not easy, though, the solution of other problems arising as a result of the philosophy upon which the establishment of a coronary care unit was based. The lack of trained personnel, especially nurses, was in itself a problem which made the premise of the establishment of the unit invalid. Such apparently small facts as electrical wiring, safe grounding, proper lighting, strategic location of monitors, and others, were thoroughly thought about, planned and effected. Precaution was the big safety word. We were conscious that upon working with so many machines, electric shock was a real hazard and intense teaching as well as protective measures were constantly planned and carried into practice.

What about the biggest problem of them all? Dr. Day and Dr. Meltzer were thoroughly convinced that for the success of their units one person was the most important of all, The Nurse (2), (3). They thought (and experience proved them right) that nurses were greatly needed who were especially trained in receiving and interpreting information from the electronic monitors, as well as in the art of early employment of corrective measures on each emergency situation. Their program was established. Nurses were taught to identify arrhythmias and other cardiac phenomena, and to employ life saving techniques such as electrical defibrillation.

To solve our problem, the best solution at hand was to send our nurses to a good coronary care unit in the United States. In fact, we sent a few carefully selected nurses and physicians. We were very lucky, and honored indeed, to have them trained at Dr. Schoenfeld's unit in Ohio. The basic requirements for the personnel selection was intelligence, a good dose of motivation, and an unsurpassed amount of dedication. Upon their return, training continued. The unit was unofficially opened for that purpose. Patients with all kinds of cardiac problems were admitted for intense training, resuscitation teams were formed and practiced, and policies on treatment of the coronary patient with his various complications were standardized with adequate flexibility. Manners and methods in the proper evaluation of clinical data for investigational purposes were established. By February of this year, the unit was opened. Our personnel had finally succeeded in overcoming the initial obstacles. It remained for time to test them for continued motivation, and dedication for continued training and learning.

The San Juan City Hospital serves a community of one half million people. Most of the patients are medically indigent, but frequently other patients are admitted since no patients suspected of having a myocardial infarction are refused.

The hospital has a bed capacity of 660, and 160 are devoted to the Medical Department. The intensive care unit of the Department of Medicine has 14 beds for ge-

neral intensive, and 8 beds for intensive coronary care.

Figure 1 shows the nurses' station and the central monitor system. The nurses' stations are strategically located so that from their desk the nurse may supervise the patients under their care. At present, the 8 beds devoted to coronary care are functioning. Two graduate nurses, one per four patients, are assigned in each shift. One nurse constantly checks on the central monitor while the other is assigned the other nursing procedures. There is at least one doctor, usually a third or second year resident, at all times in the unit, and at night, in the doctor's room in the unit. Attendings are on call 24 hours a day, seven days a week.

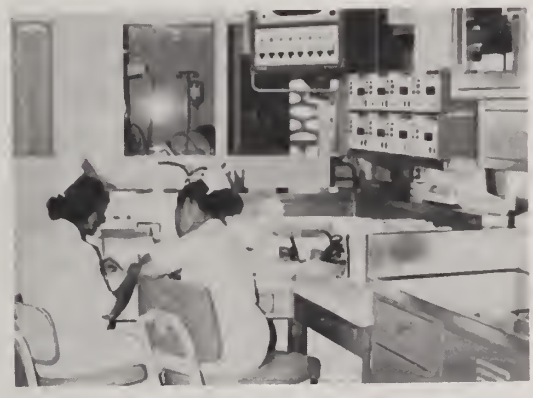


Fig. 1: Nurses' station and the central monitor system. Notice that from the station, the nurse can supervise her patients as well as the monitor system.

The next group of figures shows the equipment used. Four basic devices are used:

a) The individual unit on the patients' room (Figs. 2 and 3).

b) A remote unit at the nurse's station (Fig. 4).

c) A central monitor (Fig. 5).

d) A defibrillator and crash cart (Fig. 6).

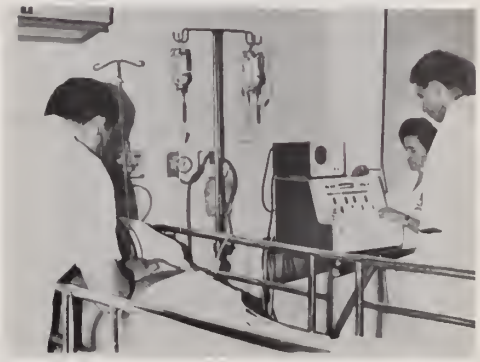


Fig. 2: Individual monitor unit at the patient's bedside.

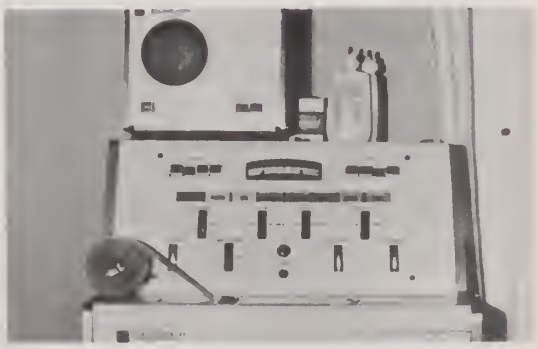


Fig. 3: Close-up of the individual monitor unit.



Fig. 4: Block of the eight remote monitor units at the nurses' station. These units are controlled by the bedside units.

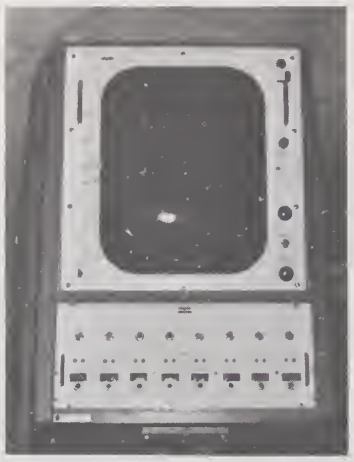


Fig. 5: Close-up view of the central monitor unit. The electrocardiogram of each patient is projected in the screen and identified by the patient's room number.



Fig. 6: View of the crashcart and defibrillator. These units are movable and can be placed in the patient's room for its use.

The individual monitor unit is connected to the patient by means of precordial electrodes. It registers cardiac activity. It can be preset to specific heart rates with an alarm system that sounds if tachycardia, bradycardia or cardiac arrest occurs. The unit is also able to take automatically electrocardiographic tracings during ten seconds every fifteen minutes or every hour, according to the preset interval of time. The remote units of the eight patients are placed in block near the central monitor at the nurse's desk. Those units work in accordance to the individual bedside unit.

Each of the individual bedside monitors has an oscilloscope which projects the patients' electrocardiogram. Each electrocardiogram is projected into the screen of the central monitor. This is the electrocardiogram which the nurse constantly watches in order to detect early arrhythmias which are not detected by the alarm system. At this point, it must be emphasized, that by this constant surveillance, early treatment for arrhythmias or block can be instituted. Because of this, in our experience, the teams are rarely confronted with the need of resuscitation. The conviction prevails that prevention of resuscitation is the chief responsibility of the unit. Necessity of resuscitation may be interpreted as a unit failure, more so if resuscitation has to be done more than once. If by any chance resuscitation measures have to be undertaken in primary cardiac standstill, the resuscitative team is brought into action by the pre-practiced methods. If the patient dies, a thorough investigation of the factors leading to this death is done, and measures taken accordingly to improve quality of medical care. One thing is obvious: "The opening of the coronary care unit in the hospital has served as a stimulus for better treatment of all hospitalized patients." That is one big advantage which is sensed in the environment but which is not accounted for upon analysis of the improved hospital statistics.

In summary, we may say that organization of a coronary care unit must be based on the following principles:

1. The nurse is the most important per-

son in the unit. Establishment of a unit without having the adequate personnel is not valid.

2. Equipment must be practical, maneuverable, modern, but not necessarily sophisticated as to the information it needs to give.
3. Policies must be established as to patient care, continuous training and learning, and above all, continuous training and teaching of the nurse.

Dr. Marchand: I hope that the discussion of Dr. Román will serve as a guideline in your thinking relative to building a coronary care unit, equipment, and nursing care. Dr. Luis G. Borrego, Attending in Medicine, and in charge of the coronary care unit has been unable to be present with us. I will have the privilege, in his absence, of presenting the current concepts of therapy, and our observations of a small series of 103 patients hospitalized in our coronary care unit.

The coronary care unit of the San Juan City Hospital was opened last February. Patients of any age, sex, and with unlimited time intervals between the onset of symptoms and admission are accepted in the unit. All admissions are decided upon by the resident assigned to the unit. In case of doubt, and if beds are available, the patient is admitted to the unit. If there is shortage of beds the resident will consult either the attending physician in charge of the unit, or the assistant chief, or the Chief of the Department for final disposition.

The patients are divided for admission into three groups: Definite, Probable and Possible Myocardial Infarctions. Any patient who on admission is in shock or in acute pulmonary edema is admitted to the general intensive care unit.

All patients remain in the unit under continuous cardiac monitoring for seven days. Should any arrhythmia occur during hospitalization in the unit, the day of onset of the complication will be considered as the first day again, and the patient will then remain in the unit for an additional seven days.

A set of standardized policies has been prepared for the management of patients and their complications. This set of policies was developed in advance by the organizing group, based on the experiences of similar groups in the United States and in Europe.

TABLE I: CLASSIFICATION OF PATIENTS ON ADMISSION

1. Definite Myocardial Infarction – typical chest pain, changing ECG with development of Q waves, and confirmatory enzyme rise.
2. Probable Myocardial Infarction – typical chest pain, changing ECG with ST-T abnormalities, and confirmatory enzyme rise.
3. Possible Myocardial Infarction – atypical chest pain, abnormal but non-specific ECG, no enzyme rise.

All physicians working in our unit are aware that these policies were set up to provide uniformity of treatment but are cognizant of the fact that they are subject to change with new experiences and research and provisions have been made to incorporate new developments as these arise.

What do we mean by myocardial infarction? On Table I are the criteria being utilized for diagnosis of proven acute myocardial infarction. They are the same criteria being followed at the New York Hospital – Cornell Medical Center. By definite myocardial infarction we mean a patient with a definite complaint, usually typical chest pain, abnormal Q waves, chang-

TABLE II: ADMISSIONS TO THE CORONARY CARE UNIT

Classification	No.	Percentage
Definite myocardial infarction	50	48
Probable myocardial infarction	15	14.5
Possible myocardial infarction	38	37.8

TABLE III: FINAL DIAGNOSIS

Classification	No.	Percentage
Definite myocardial infarction	80	77.7
Probable myocardial infarction	5	4.9
Other diagnoses (Angina pectoris, coronary insufficiency, emboli, etc.,)	18	17.4

ing electrocardiogram with S-T and T wave abnormalities but no abnormal Q wave, and enzyme rise. It is believed that these two groups of patients have acute myocardial infarction. The third group, possible myocardial infarction, is the patient with an atypical clinical picture, non-specific electrocardiographic changes, and no confirmatory enzyme rise.

In our small series (Table II), we have admitted during the first eight month period of operation 103 patients who initially were classified as 50 patients with definite, 15 with probable, and 38 with possible myocardial infarction. The unit is especially concerned with the patient at first appearing to be probable or possible myocardial infarction. The interesting point is that, of the 38 patients who had an atypical clinical picture, very little electrocardiographic changes on admission and with no elevation of enzymes, seventeen of these patients proved later on to suffer from definite myocardial infarction, and one of them died. Of the 15 patients with admission diagnosis of probable myocardial infarction, 12 had established infarction by our criteria as final diagnosis.

Upon discharge (Table III) the classification of our patients revealed 80 with definite, and five patients with probable infarctions. A sixth (18) of patients admitted to the coronary care unit were found to have other diagnoses. These belonged to the group of 38 patients admitted as possible infarctions, but on later evaluation turned to have angina pectoris, pulmonary emboli, psychiatric problems, etc.

I want to call your attention to the fact that a substantial error is introduced by the exclusion of patients in whom the diagnosis is in doubt. He is the patient with an atypical picture, of pain that may be epigastric and normal electrocardiogram, which has been interpreted as a problem of "indigestion". We prefer to err by commission rather than by omission, and this serves as a guideline in the admission policies of the unit.

The age distribution of patients is shown in Table IV. The patient 20 years old suffered a blow in the chest with a softball, and a few days later was seized with a severe substernal pain. The initial electrocardiogram showed non-specific changes, but serial tracings and enzymes elevation proved to have a definite infarction. In our small series, patients 50 to 70 years of age had the highest incidence. No age appears to escape infarction. In our indigent population there appears to be a 3:1 ratio of male to female.

The electrical instability of the heart in a patient with acute myocardial infarction is

TABLE IV: AGE AND SEX DISTRIBUTION OF PATIENTS WITH DEFINITE AND PROBABLE MYOCARDIAL INFARCTION

Age	Sex	
	Male	*Female*
20 – 30	1	
30 – 40	2	1
40 – 50	6	5
50 – 60	21	7
60 – 70	21	8
70 – 80	3	3
80 – 90	2	2
90+		2
Totals	56	28

TABLE V: ARRHYTHMIAS IN MONITORED PATIENTS WITH DEFINITE AND PROBABLE MYOCARDIAL INFARCTION

Type of Arrhythmia	No.	Percentage
Premature atrial beats	5	5.8
Premature ventricular beats	28	32.9
Premature nodal beats	1	1.2
Sinus bradycardia	7	8.2
Second degree A-V block	4	3.8
Third degree A-V block	2	2.4
Right bundle branch block	3	3.5
Left bundle branch block	2	2.4
Atrial fibrillation	2	2.4
Paroxysmal atrial tachycardia	1	1.2
Ventricular tachycardia	7	8.2
Ventricular fibrillation	7	8.2

responsible for the frequent complications of arrhythmias (Table V), pump failure with shock, and congestive heart failure. It has been reported that 90 percent of patients with acute infarction have arrhythmias. In our small series we had only 65 percent.

Premature ventricular contractions are the most important of these arrhythmias; they have the highest incidence (70 percent), are short lasting, will evoke ventricular fibrillation and death if untreated, while being very easily controlled with therapy. Premature ventricular beats are treated if they fulfill certain criteria: 1) Runs of 2 or more beats, 2) A frequency of more than 5 per minute, 3) Multifocal ventricular premature beats, 4) When they interrupt the T wave (i.e. a Q-R'/Q-T ratio of less than 0.85).

I would like to call your attention to ventricular premature contractions in a patient with bradycardia. The use of lidocaine or pronestyl to correct these premature beats in tachycardia is contraindicated in bradycardia. Antiarrhythmic drugs, without prior acceleration in heart rate in bradycardia, may provoke more serious ventricular arrhythmias.

Of interest in our series was the absence of first degree A-V block. We had only two cases of complete A-V block. In one patient a temporary pacemaker was successful while in the unit, but he died few days later while in the general medical ward from another acute myocardial infarction. The other patient with complete A-V block responded promptly to the administration of intravenous Isuprel®.

Twelve patients died in the unit and 5 after leaving the unit (Table VI) but while still in the medical wards, accounting for, in such a small series, for a mortality of about 20 percent.

Table VII shows an analysis of the 12 deaths in the unit. I would like to remind you that we accustom, when the patient is

TABLE VI: DEATHS IN 85 PATIENTS WITH DEFINITE AND PROBABLE MYOCARDIAL INFARCTION

	No.	Percentage
Deaths in the Unit	12	14.1
Deaths in the Hospital	5	5.9
Total -	17	20.0

first admitted, to assess the clinical picture of the patient. On admission we check for the presence of: 1) arrhythmias, 2) left ventricular failure, 3) pulmonary edema, 4) the presence of shock. I think these 4 parameters are of extreme prognostic significance. We attempted resuscitation in 7 patients and they all died. All patients in acute pulmonary edema and shock died. It appears that with the control of VPBs and short runs of ventricular tachycardia we were able to prevent catastrophic arrhythmic complications such as sustained ventricular tachycardia and ventricular fibrillation. What I mean to say is that our deaths were chiefly due to "pump failure". Another point of interest was that one of the patients dying outside the unit was found to have a ruptured chorda tendinae and of those dying in the unit, two had a ruptured septum, and another a ruptured papillary muscle. The meaning of this is difficult to ascertain...Is it a coincidence?

In the next Table VIII we indicate the analysis of 5 patients dying in the wards after leaving the unit.

It is impossible to reach any conclusions from a small series. We depend on statistics. But we know that statistics remind us of a bikini! "A bikini shows what is suggestive and conceals what is vital". In our hospital, for many years, our mortality had been approximately 40 percent. We have reported 85 patients with a 20 percent mortality. The incidence of arrhythmia in our patients is lower than reported, and this stimulates us to "strive on" in order to improve our monitoring techniques. We appear to have prevented catastrophic primary arrhythmias. Shock and pulmonary edema present a serious challenge.

Our next speaker will be Dr. Schoenfeld who will discuss his wide experience, and secondly I would like Dr. Schoenfeld to make some comments about the responsibility and relations of a coronary care unit to the community, and if possible what he has to say about the future of this unit.

Dr. Schoenfeld:* I would just like to point out that in the States there are 2,000,000 heart attacks a year. At least 500,000 patients die of heart attack in the States each year. This is the single leading cause of death throughout the Western Hemisphere as far as we can tell. I would like to discuss the experiences in Framingham, Massachusetts. You know, they are setting aside the whole town who has agreed to let the Public Health Service just watch and see what happens as far as heart disease is concerned. The patients are checked once a year to see if there have been any changes in their status. I guess there are one or two important findings. The first one is concerned with how the patient first showed that he had coronary heart disease. They found that 14 percent of them for the first time knew that they had heart disease was when they died suddenly.

* - *Professor of Medicine, Ohio State University Medical School.*

TABLE VII: ANALYSIS OF 12 DEATHS IN THE CORONARY CARE UNIT

Age Yrs.)	Time Interval Symptoms-Admission	Time Interval Admission-Death	Admission Clinical Status	Mode of Death	Autopsy
67	3 days	1 hour 20 minutes	2°A-V block	Ventricular tachycardia Ventricular fibrillation	Acute left ventricle myocardial Infarct
61	24 hours	3 days	Premature ventricular Contractions S. A. bradycardia Diabetes	Acute pulmonary edema Shock	Not done
68	24 hours	4 hours	Premature ventricular Contractions Congestive heart Failure Shock	Congestive heart Failure Shock	Recent and acute anterolateral Myocardial infarct Pulmonary congestion
67	3 days	7 days	Premature ventricular Contractions 2°A-V block Right bundle branch Block Congestive heart Failure	Ventricular tachycardia Ventricular fibrillation	Acute anterolateral myocardial Infarct
64	8 hours	1 hour 30 minutes	Acute pulmonary Edema	Acute pulmonary edema Ventricular fibrillation	Lateral myocardial infarct Pulmonary edema Active pulmonary tuberculosis
74	2 days	3 days	Right bundle branch block	Ventricular tachycardia Shock	Anteroseptal myocardial infarct Ruptured interventricular septum Pulmonary congestion
50	4 hours	9 days	Congestive heart failure	Shock	Acute anterior infarct
35	5 hours	9 days	Premature ventricular Contractions Congestive heart failure	Shock	Acute anterolateral myocardial infarct Ruptured interventricular septum Pulmonary congestion
30	3 1/2 hours	8 days	Premature ventricular Contractions Senile emphysema	Shock	Not done
54	Unknown	2 days 15 hours	Premature ventricular Contractions Ventricular tachycardia Cerebrovascular accident Diabetes	Shock Ventricular Fibrillation	Acute anterior infarct
2	48 hours	6 hours	S. A. bradycardia	Shock	Acute anteroseptal infarct Ruptured chorda tendinae Pulmonary congestion
6	24 hours	4 hours	Bronchial asthma Intractable chest pain	Acute pulmonary edema	Acute anterolateral infarct

TABLE VIII: ANALYSIS OF 5 DEATHS IN THE HOSPITAL WARDS

Age (Yrs.)	Time Interval Symptoms-Admission	Time Interval Admission-Death	Admission Clinical Status	Mode of Death	Autopsy
85	7 days	11 days	Premature ventricular Contractions Congestive heart Failure	Congestive heart failure	Not done
75	4 hours	19 days	Premature ventricular Contractions	Shock Ventricular fibrillation	Not done
64	5 hours	11 days	Premature ventricular Contractions	Congestive heart failure	Not done
72	3 days	9 days	Congestive heart Failure	Acute pulmonary edema Shock	Acute posterior infarct Ruptured papillary muscle Pulmonary congestion
90	3 days	19 days	Premature ventricular Contractions 3° A-V block	Ventricular tachycardia Ventricular fibrillation Shock	Recent posterior infarct Acute infarct at interventricular Septum Pulmonary congestion

There were some deciding factors in the death of 800 patients in 9 different hospitals. In 800 patients the percentage of death was classified by the day on which it occurred, and it was found that the great majority of death occurs within the first three days. So we have a disease where the incidence is extremely high; a disease in which death is most liable to occur during the first three days of illness. Treatment for this type of death has long been available. As far back as 1929 physiologists knew how to apply defibrillation in experimental animals.

Dr. Zoll introduced the technique for electric shock treatment of ventricular fibrillation just following World War II. At the same time in Baltimore the technique of cardiac massage was being developed to its full extent. As soon as this information became available, it became possible to launch a new attack on the mortality due to myocardial infarction. As Dr. Marchand told you the coronary care units were opened by Dr. Hughes Day in Kansas City and by Dr. Brown in Toronto in 1961 or 62. Now, I figure it important to point out that Dr. Day's hospital is not a large university hospital. It is a hospital of a private nature supported by the church with a very limited house staff. He told me that when he opened his first coronary care unit, he had no interns. I guess this is significant for us because we have to remember that a good doctor in practice no matter where he may be can still contribute significantly.

I would like to tell you some of our ex-

periences. We opened our coronary care unit 3-1/2 years ago. Columbus, Ohio, is a city of about 700,000 people including the suburbs. When I left there on Monday the temperature was 38; and we have a lot of cold weather which is important in coronary artery disease. There are now in our city 3 other coronary care units in private hospitals. My hospital, being a university hospital, serves as a city hospital somewhat and it has about 350 beds not counting pediatrics, tuberculosis and psychiatric beds. Our coronary care unit has 8 beds in it and it was developed by simply taking over 8 private rooms and one 4 bed ward. We had to work within the existing architecture. We have in this unit the same monitoring equipment described by Dr. Román. The admission policies: We admit all patients, i.e., anyone who has chest pain, one who comes to our emergency room and is referred is accepted on our unit, if the doctor has a reasonable suspicion that the patient has a myocardial infarct. We tell our interns and residents to admit people if they have any doubt in their minds. We tell them to not let the electrocardiogram decide whether a patient is admitted because we feel that a normal electrocardiogram does not mean that the patient didn't have a heart attack because you may have myocardial infarction with a normal electrocardiogram. We feel that we must continue to be good clinicians, and to talk to our patients carefully and examine them carefully and on this basis decide whether they may have had a heart attack. If we go by the electrocardiogram we may send home a patient who will die. This happened to us this past summer. A patient presented to our emergency room and said: "I've got bad indigestion in the pit of my stomach." The intern thought of a heart attack, took an electrocardiogram and it was normal. He said: "You go on home. I will give you some Alndrox". When the patient got to the parking lot to get his car to drive home, he dropped the Alndrox because he had ventricular fibrillation and died of an acute heart attack. I think this is one pitfall which we must not have. Our patients are admitted quickly to our coronary care unit. The coronary care unit is on the 11th floor of the hospital; the emergency room is on the first floor. Our elevators run on Puerto Rican time. We have certain problems which must be taken into account. We have installed a telephone on the elevator and it is possible to call up the operator and tell her to hurry. This is important because our most recent success of resuscitation occurred three minutes after the patient arrived on the coronary care unit. I think it's important to get these people in quickly. One of the most interesting examples of why this is so I think occurred in Norway. They told me about the experiences in a coronary care unit in Norway. In the coronary care unit in Norway, the death rate is very low, almost 10 percent or below in most of them. I asked why and they told me: "Well the patient usually must ski 3 to 4 hours to reach the coronary care unit". This is one sure way to keep your admission rate very low. I don't know your situation in Puerto Rico; you may have to climb some mountains I guess, or swim a bit. But these things must be taken into consideration because a fair number of patients die en route to the hospital. There are efforts now being made to see how we could avoid this. In Ireland an ambulance has been equipped as portable coronary care unit. With this ambulance they have resuscitated in one year 12 people who died in the ambulance. Our patients stay in the coronary care unit 5 to 7 days, then they are moved to other areas of the hospital. We have had some people who die after leaving the unit also. This is a universal experience through-

out the world. The primary care of the patient is left to the intern and resident with the director of the coronary care unit, myself, or with the senior research fellow. We do not assume control of all patients. The patients are left under the care of their family physician if they are able to pay for his service. We do not interfere with routine management but we do reserve the right to step in when there is an emergency. This has not resulted in any controversy between private practicing physicians and the doctors in the hospital. As a matter of fact it has increased the amount of good feelings between all doctors concerned. The house staff, interns and residents, are instructed on arrhythmias detected by the nurses. If the nurse finds there is an arrhythmia we tell the interns and residents that they have to reach a decision on how to treat within 3 to 5 minutes. Of course if there is a dangerous fatal arrhythmia like cardiac arrest, the people in our unit have been carefully trained to do the resuscitation.

I would like to emphasize some of our diagnostic observations in the coronary care unit. There are patients who come to the hospital with chest pain, but it turned out they didn't have myocardial infarction. They had angina pectoris, hiatal hernia, pulmonary emboli, etc., and this is a significant problem of admission. We move these people out fairly quickly, but I know of no way this situation can be avoided. Once the decision is made to operate a coronary care unit, this factor must be taken into account. Unfortunately we don't know now a good way to diagnose myocardial infarction within the first hour or two after it begins.

During the first year our mortality rate was 32 percent; before the coronary care unit it had been 45 to 50 percent. During the second year of our coronary care unit we said: "Wonderful! As our mortality rate dropped down to 18 percent". But then the next year we were depressed because we were back up to 28 percent. So I want to point here that we must be very cautious in interpreting our results.

We have resuscitated 10 people in over 3 years. These are people who died and were brought back. If they had been anywhere else in my hospital, they would have died. We found the resuscitation successful if the patient was able to be discharged from the hospital and return to his former state of health. If he doesn't do this, it is not a success. We have resuscitated a number of people who died several days or weeks later. We also have treated a lot of heart block because we put in these permanent cardiac pacemakers. I think that some day our coronary care unit probably will have facilities for this, but this may be well on in the future. A significant number of these patients are resuscitated.

Complex arrhythmias not due to myocardial infarction are admitted to the coronary care unit only if there is space. There is considerable pressure to admit these people because their electrocardiograms look so bad. But their mortality rate is low, we do not resuscitate many of these people and they require a lot of care. You have to fight to keep these patients out of the unit.

The resuscitation of a number of people that we have achieved justifies our having the unit; there are a number of people who are alive who would not be alive otherwise. The same is true here in your unit in San Juan City Hospital. In the short time it has been opened, it has already resulted in the saving of a number of lives. I think this alone justifies all the efforts and the expenses as well.

We have learned from our experience some-

thing about prevention. In this we are chiefly concerned with arrhythmias. We have an awful lot of arrhythmias. Of our patients 77 percent have premature ventricular beats. We teach our staff that this is an emergency. Something must be done immediately. Ventricular tachycardia occurs in 30 percent of our patients; if they only last a few seconds, they succumb. Atrial fibrillation is fairly common. Heart block may cause death and occurs in 10 to 20 percent of all our patients. A number of patients, 15 to 20 percent, have some degree of heart failure. This must be taken care of. Ventricular fibrillation is the most common cause of death; 8 percent of our patients will die suddenly due to ventricular fibrillation. We should be able to say therefore, that we should be able to reduce our mortality 8 percent if we are good enough.

The arrhythmias may be very brief and must be recognized by the nurse; the machine won't do it. We must have our hospital attendants on the alert. The doctor must be prepared, must be trained to know what to do in the event of such emergencies and must begin to take preventive steps.

Now I would like to comment briefly on the coronary care unit of the San Juan City Hospital. First, I am proud of this unit and hope that you are too. It is the first unit in the Caribbean, and the first unit, in any situation I know, where Spanish is spoken. Its results have been excellent. I think this is a good coronary care unit as any that I know of. I think the patients are a little slow in getting into the hospital and this may affect the mortality. There may be a higher mortality when patients start to arrive faster. I do not know.

Now I will like to go into defining responsibilities as I see them, both here and in other parts of the world. First I think that this unit will be provided in many hospitals throughout the countries of the world. I feel that first of all hospitals must have provided the important good basic medical care which is necessary for all people. I think the first thing the hospital must have is good doctors, good nurses, good X-ray, good clinical chemistry laboratory. I think these things come first if we like to provide a high level of medical care. Then I think that the coronary care unit may be put in next along with intensive care units of other sorts. I think that doctors and medical societies should begin to find out about their hospitals. They may decide that their hospital is not ready for a coronary care unit as yet. But they should look to this situation because in the future, we don't know the time, maybe a year, maybe ten years, maybe 20 years, when they won't want to have a coronary care unit and perhaps the time to find out is now. I think that medical societies, government, private foundations should be prepared to lend support. This is an expensive business to them but certain expenses and help will be needed. I think the first step to open a coronary care unit is not to buy the machinery. I do not think anyone should buy machinery until they have trained their nurses, until they have trained their doctors; because doctors need training too. We all cannot know everything, we can't know everything in medicine today, it's impossible. Sometimes I feel like I don't know anything. But we must be trained, doctors as well as nurses. The first step is training and then perhaps the purchase of equipment. Because you see, the machines will not do anything, machines do nothing to save patients if the people are not trained to use them, the mere fact of purchasing a machine accomplishes nothing. I have seen it done in other places where people were very disappointed because no patients had been saved. The machines do not take the place of a well trained nurse or doctor. The nurse recognizes an arrhythmia and nurses can give resuscitation.

In Ohio there is a small rural hospital that has a coronary care unit. There are no doctors in that hospital after summer time, but there are some doctors who have been training nurses dedicated to working in a coronary care unit. They have provided the training and a strong motivation for the nurses. In this particular coronary care unit that I know about, there have been 6 people resuscitated by the nurses alone in one year. So I think this is not necessarily something alone for only the big hospitals. Remember the first unit opened was in a small community hospital. So I think it requires doctors with dedication who are willing to take some additional training in cardiology. He must be willing to train his nurses even if it will require a sacrifice from him; he may not be able to enjoy as much private practice as other people. The nursing personnel must be dedicated and willing to work hard. If they are not paid adequately, I think they should get extra pay because their responsibilities are tremendous. I think in the States, however, it is possible to bring the type of special medical care to our patients that we all want. I think this can be done with a great deal of pleasure and excitement on the part of the doctors involved and without creating any great controversies. I think this problem needs to be attacked. We lose valuable people this way when death could be prevented so easily.

I hope that you have benefited from my presence. I have certainly benefited from being here, and have learned more than I have taught. Thank you very much.

Dr. Marchand: The paper is open for questions and discussion.

Question: What do you mean by pump failure?

Answer: By pump failure we mean the concurrent clinical manifestation of both congestive heart failure and shock. It carries a very poor prognosis and it is most difficult to manage.

Question: In acute myocardial infarction, why do you differentiate between hypotension and shock?

Answer: It is very difficult to differentiate hypotension and shock. There is no uniform agreement on the concepts of cardiogenic shock. For practical purposes, shock is present when there is a systolic blood pressure less than 90mm Hg with evidence of peripheral vasoconstriction including sweating, cold skin, confused sensorium and oliguria. Results of treatment still remain very poor (80-90 percent mortality). We follow partly Dr. Lawrence E. Meltzer's therapeutic program consisting of early treatment, prompt correction of any existing arrhythmias, aggressive digitalization with oubain and intravenous Isuprel® due to their potent inotropic action, and correction of lactic acid acidosis with sodium bicarbonate or THAM if available. Hypotension doesn't mean shock, but demands very close observation.

Question: When and how do you digitalize in acute myocardial infarction?

Answer: Clinical manifestation of congestive heart failure has been reported by some investigators to occur in 60 percent of patients and another 30 percent will have radiologic evidence without an overt clinical picture. We have never learned what a full digitalizing dose is. In the case of digitalis as with many other drugs there is a strikingly wide range in individual sensitivity and response. A maintenance dose for one patient may be lethal for another and yet prove ineffective in a third. In the patient with acute myocardial

infarction we proceed with caution. Patients are underdigitalized (3/4 digitalizing dose) to protect them from at least partly iatrogenic arrhythmias. Some people consider that with adequate digitalization at the right time, you may help to prevent pump failure later. In other patients, a patient doing well but with basal rales, we prefer oral digoxin.

Question: What is the present status of anticoagulants?

Answer: The pendulum is moving again, and at present anticoagulants are being used only in selected cases. Indications for their use may be intractable chest pain, congestive heart failure, shock, previous infarcts. Definite indications are thrombophlebitis and pulmonary emboli. Intravenous heparin is the one of choice.

Dr. Marchand: An attempt has been made to present the image of a coronary care unit. Doing so, we may be meeting our responsibilities in warning physicians, hospitals and the community about uncontrolled proliferation leading to more expenses and frustrating results. It is the very essence of preventive medicine to apply prophylactic measures to many in order to protect the few who may be afflicted. Prevention is the philosophy this unit. Many questions still remain to be answered. Thank you.

PULMONARY EMBOLISM
CLINICAL STUDIES

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In recent years there has developed a great enthusiasm in the study of pulmonary embolism. Because great progress has been made in the surgical treatment of the potentially lethal form, greater emphasis has been given to the early diagnosis of the condition. New diagnostic methods have been discovered, others have been refined, and today the physician possesses a diagnostic and therapeutic armamentarium with which he can successfully manage the situation. Some of these tests are old and simple, others are new and sophisticated, but still none of them can match the one single factor which has proved to be the most valuable of all: a high index of suspicion.

Material and Methods

Our study was performed during three periods:

1. April 1966 to September 1966: During this period the diagnosis was done on the basis of the clinical picture, chest X ray, electrocardiogram and the laboratory triad suggested by Wacker et al (1). This triad consists on determination of serum lactic acid dehydrogenase (LAD), serum bilirubin, and serum glutamic oxaloacetic transaminase (SGOT). Normal values in our laboratory are as follows: LAD, 500 Sigma units; total serum bilirubin, 1 mg. percent: SGOT, 35 Sigma units. An elevated LAD, elevated bilirubin and normal SGOT is suggestive of pulmonary embolism (1).

2. September 1966 to February 1967: As above plus confirmation by pulmonary arteriography.

3. February 1967 to October 1967: As above plus the use of pulmonary scan.

During the same period (April 1966 to October 1967) we reviewed all the autopsies done in adults dying in the hospital. A total of 225 autopsies were reviewed. It was our purpose to determine the incidence of significant pulmonary embolism in our autopsy material and to determine the antemortem diagnostic accuracy.

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Presented in part at the Puerto Rico Medical Association Meeting, November 16, 1967.

Results

Table I shows the method of diagnosis in our study. Forty-six of the 76 cases were confirmed by: autopsy (19 cases), pulmonary arteriography alone (4 cases), by pulmonary scanning alone (16 cases), and by both, pulmonary arteriography and scanning (7 cases). Diagnosis in the remaining 30 cases was done by the highly suggestive clinical picture and further strengthened by the electrocardiogram, chest X-ray and Wacker's laboratory triad. The 10 cases found at autopsy were found among 225 autopsies reviewed (8.5 percent). Only one of the cases diagnosed by autopsy was diagnosed correctly pre-mortem. The other 18 cases had the embolic episodes while suffering from debilitating diseases such as sepsis, cerebrovascular accidents, carcinomatosis, etc., which masked the picture.

TABLE I: METHOD OF DIAGNOSIS

Method	No.	Percentage
Highly suggestive clinical picture corroborated by ECG, chest X-ray and Wacker's laboratory triad (Scan or arteriography not done)	30	39
Autopsy *	19	25
Clinical picture corroborated by pulmonary scanning alone (arteriography not done)	16	22
Corroboration by both pulmonary arteriography and scanning	7	9
Corroborated by pulmonary arteriography alone (scan not done)	4	5

** - The autopsy study was done in retrospect and included the autopsies done in our hospital during the time the study was done. (April 1966 to October 1967)*

Table II enumerates the clinical situation leading us to suspect the diagnosis. The typical attack occurred in 25 percent of the cases. Detailed description of the several clinical patterns listed in this table is in preparation.

Fifty five of the 76 patients had serum lactic dehydrogenase performed. Forty nine (87 percent) were found to have values above 550 units. Values were elevated by 24 hours after onset of symptoms and normal by one week unless the patient had evidence of recurrent emboli.

Seventeen out of 51 patients had elevated serum glutamic oxaloacetic transaminase levels. Most of these patients had evidence of refractory congestive heart failure, frank failure precipitated by the embolus, or shock. Otherwise, uncomplicated cases had normal SGOT. Total bilirubin levels above 1 mg. percent, were seen in 16 of 43 patients (38 percent).

Table III shows the most important signs and symptoms found in our series. All patients showed tachypnea. No evaluation was done of the second pulmonic sound because of the difficulty in determining the second pulmonic from the second aortic sound without the aid of phonocardiogram (2). Phlebitis was present in only 30 percent of the cases. In some of them, the diagnosis of phlebitis was done by the tourniquet test, eliciting a Homan's sign, or by differences on the circumference of the legs at the calves. In some of the patients, the evidence of phlebitis appeared after the patient had the attack.

Wheezing was detected in 11 percent of the cases. In some of these cases, the picture resembled bronchial asthma because the patients had history of bronchial asthma in their childhood and because of the intensity of the wheezing.

TABLE II: CLINICAL SITUATIONS LEADING TO *SUSPICION* OF PULMONARY EMBOLISM

The typical attack
Intractable congestive heart failure
Bilateral bronchopneumonia
Pneumonia with atypical onset or in patients with known predisposition to embolism, like after surgery, delivery, cardiac disease, etc.
Asthma
a) with atypical onset
b) developing simultaneously with chest pain
c) *de novo* in an adult
d) of cardiac type (cardiac asthma)
e) responsive to heparin
f) unilateral wheezing
g) patients with other clinical signs of embolism such as haemotysis, phlebitis, etc.
h) with laboratory abnormalities suggesting pulmonary embolism such as EKG changes, abnormal chest X-ray, abnormal LDH, etc.
i) abnormal pulmonary scan
Pulmonary edema
Shock of undetermined origin
Chest pain
Hyperventilation syndrome in a cardiac
Phlebitis with respiratory signs or symptoms
Arrhythmias of sudden onset
Tachycardia of unknown origin
Syncope
Cerebral thrombosis with neurological deficit
Right upper quadrant pain
Sudden death

TABLE III: INCIDENCE OF SIGNS AND SYMPTOMS

Sign or Symptom	No.	Percentage
Tachypnea	76	100
Dyspnea	70	90
Chest pain		48
Pleuritic	24	
Anginal	3	
Anginal with inspiratory accentuation	3	
Other	7	
Phlebitis	22	30
Haemotysis	12	16
Congestive Failure	11	15
Wheezing	9	11
Shock	2	3

TABLE IV: PROBABLE PREDISPOSING CONDITIONS

Predisposing Condition	Incidence
Leg phlebitis	30 percent
Malnutrition, cancer, etc.	14
Congestive heart failure	13
Surgery	7
Varicosities in legs	6
Pelvic thrombophlebitis	1.5
Fractures	0

TABLE V: UNDERLYING DISEASE

Disease	No.	Percentage
Arteriosclerotic heart disease	15	20
Rheumatic heart disease	5	6.5
Diabetes mellitus	7	9
Carcinomatosis	4	5.3
Cerebrovascular disease	4	5.3
Idiopathic heart disease	1	1.5
Not present or not determined	40	52.4

Pleuritic chest pain was the most frequent type of pain. A yet undescribed pain was observed: an anginal type of pain accentuated by inspiration. Shock was present in two cases. In one of those patients the anginal type of pain and the electrocardiogram changes lead the physician suspect myocardial infarction. Autopsy disclosed several pulmonary emboli.

Table IV shows the probable predisposing conditions. Thrombophlebitis in the absence of other predisposing conditions was observed in 30 percent of the cases. The next important conditions were congestive heart failure, and malnutrition, cancer and cerebrovascular accident combined.

Table V shows the underlying disease in our series. Heart disease was present in 28 percent of the patients; diabetes mellitus, in 9 percent.

Electrocardiogram was performed in 47 patients (Table VI). Of these, 89.4 percent were abnormal and 10.6 percent were normal. However, only 38 percent of the abnormals were suggestive of acute cor pulmonale. The most common changes were the so called P-pulmonale and inverted T waves over the right precordial leads, (Table VII). These changes were of short duration, usually lasting from 24 hours to a week or two.

Chest X-rays were done in 51 patients (Table VIII). It was normal in 36 percent of

TABLE VI: ELECTROCARDIOGRAM

ECG	No.	Percentage
EKG done	47	100
Abnormal without evidence of pulmonary embolism	24	51
Abnormal with evidence of pulmonary embolism	18	38
Normal	5	10

TABLE VII: ELECTROCARDIOGRAM SUGGESTIVE OF PULMONARY EMBOLISM

Findings	No.
Inverted T wave in right precordial leads	8
P pulmonale	7
Prominent S in V_5 V_6	4
S_1 Q_3 pattern	2
Q_3 T_3 pattern	2
Prominent R in V_1	1

TABLE VIII: CHEST X-RAYS

Finding	No.	Percentage
Total cases X-ray done	51	100
Normal Chest X-ray	19	36
Abnormal without evidence of pulmonary embolism	18	35
Abnormal with evidence of pulmonary embolism	14	29

TABLE IX: PULMONARY LESIONS BY X-RAY SUGGESTIVE OF PULMONARY EMBOLISM

Observation	No.	Percentage
Blunting of costophrenic angle	7	38
Pleural effusion	4	25
Pneumonitis	5	24
Westermark-Torrance sign	2	10
Descent of small fissure	1	5
Total cases	19	

TABLE X: FREQUENCY OF PULMONARY EMBOLISM IN DIFFERENT CLINICAL CONDITIONS

Condition	Frequency
Myocardial infarction	8 percent (4)
Sudden death	5 percent (5)
Acute pulmonary disease in hospital practice	Most common (6)
Autopsies, adults, general	2.8 percent (3) to 25 percent (7)
Cause of post operative death	0.1 percent (3) to 5 percent (8)
Incidence in hospitalized patients with fractures	Most common cause of death (9)

the cases. In only 29 percent was the X-ray abnormal and suggestive of pulmonary embolism.

Table IX lists some of the chest X-ray changes seen in pulmonary embolism.

Discussion

Pulmonary embolism is the great impersonator. The clinical picture may vary from a mild sensation of "uneasiness" which maybe be interpreted as of psychophysiological origin, to the very rampant and dramatic picture of shock, or to the quiet but dreadful picture of sudden death (Table II).

In only 30 percent of the cases is the picture typical of pulmonary embolism (3). In the remaining 70 percent, the patient exhibits signs and symptoms, which when combined with other factors and a high index of suspicion make the diagnosis possible.

Table X, (References 4-9), shows the frequency of pulmonary embolism in different clinical conditions.

Laboratory Tests:

In 1961 Wacker et al suggested that the use of LAD, SGOT, and serum bilirubin was of great help in the diagnosis of pulmonary embolism, if the LAD was elevated, the SGOT was normal and the bilirubin was elevated (1).

TABLE XI: SUMMARY OF EIGHT CASES PRESENTING ASTHMA

Case	Age	History of Asthma	Sex	SGOT	LDH	Bilirubin	EKG	Phlebitis	Lung Scan	Pulmonary Arteriogram	Chest X-Ray
1	26	No	F	27	1150	1 mg.	P pulmonale	Yes	Not done	Not done	LLL infiltrate
2	64	No	F	--	1240	1.3 mg.	P pulmonale	?	Not done	Not done	Oliguemia Left lung, Pleonemia Right lung
3	67	No	F	25	750	.5 mg.	T wave changes, non specific	Yes	Not done	Not done	Pneumonia left, base
4	74	Yes	F	28	1290	--	Deep S V_5, V_6	No	Multiple cold areas	Not done	Pneumonitis right base
5	45	Yes	F	32	770	1.2 mg.	T wave changes, non specific	Yes	Not done	Not done	Negative
6	26	Yes	F	27	1200	.8 mg.	P pulmonale	Yes	Not done	Not done	Pneumonitis left base
7	45	Yes	F	55	720	--	P pulmonale, ischemic changes	Yes	Abnormal	Abnormal	Westermark-Torrance sign
8	56	Yes	F	66	950	--	Deep S V_5, V_6	Yes	Abnormal	Abnormal	Pneumonitis

The main use of this diagnostic laboratory triad is in the differentiation of pulmonary embolism from myocardial infarction. In myocardial infarction, the LAD elevation occurs later than in pulmonary embolism; SGOT elevation occurs more frequently and earlier in myocardial infarction. Serum bilirubin, if elevated, points to pulmonary embolism. The value of these determinations in differentiating pulmonary embolism from pneumonia has been challenged (10).

The source of the LAD elevation in pulmonary embolism has not been settled. Different studies have revealed elevations in different LAD isoenzymes suggesting that different tissues may contribute to the elevation.

In a study of lung homogenates, Cohen et al (11) found that isolated injury of human lung might result in the appearance of a beta-gamma LAD isoenzyme enrichment of the blood. However, of 7 cases with abnormal LAD, 3 had beta-gamma abnormality, 3 had alpha abnormality and one had both. The beta-gamma abnormality was seen only when there was evidence of severe hepatic congestion. The alpha abnormality presumably derived from an injured myocardium and/or from destroyed red blood cells at the site of the infarct or pseudoinfarct (11). The serum bilirubin elevation has been proposed to be due to red blood cell destruction at the site of the infarct and/or to impaired hepatic function due to congestion.

The electrocardiogram, if suggestive of pulmonary embolism, is of value. It has been reported that less than 20 percent of cases with pulmonary embolism show changes indicative of it (12). In our series, changes suggestive of pulmonary embolism occurred in 38 percent. (Figures 1 and 2 and Table VII).

The chest X-ray has been reported to be indicative of pulmonary embolism in about

50 percent of cases (6). In our experience the most frequent findings were pneumonitis, pleural effusion and blunting of a costophrenic angle by fluid or by a pneumonitis (Table IX, Figure 3 and 4). The presence of the Westermark-Torrance (13) sign was noted in two cases. It is characterized by an increased area of radioluceney on the chest X-ray related to the decreased vascularity (oligemia) in the area, secondary to the vascular obstruction (Figure 5). Descent of the small fissure and elevation of the diaphragm were observed in one case (Figure 6). Such changes are related to the decreased ventilation and perfussion of the affected lung tissue (14).

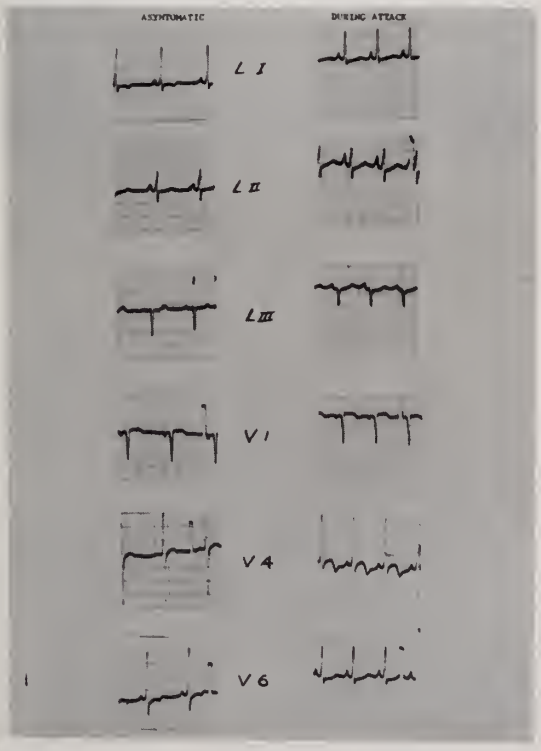


Fig. 1: Acute cor pulmonale as shown by prominent, peaked P waves; ischemic T wave changes and ST segment coving. The presenting clinical picture in this patient was acute pulmonary edema. Pulmonary embolism was corroborated by pulmonary scan and arteriography.

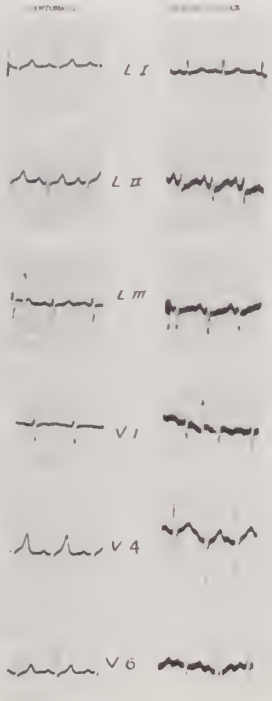


Fig. 2: Electrocardiogram demonstrating prominent P waves, righward deviation of the Paxis, tachycardia and clockwise rotation of the heart in the horizontal axis as demonstrated by prominent S waves in V_4 - V_6 as compared to asymtomatic tracing (left).

Symptoms and Signs:

Dyspnea and tachypnea were important aspects of the clinical picture. In the conscious patient dyspnea and tachypnea, and in the stupurous or comatose patient, tachypnea, were always present. In the comatose patient, tachypnea may be confused with the type of respiration seen in cerebral damage, acidosis, or congestive heart failure. All autopsied patients in which the diagnosis of pulmonary embolism had not been suspected pre-mortem had had tachypnea as part of the terminal picture.



Fig. 3: Roentgenogram of the chest showing blunting of left costophrenic angle by pneumonitis or fluid.

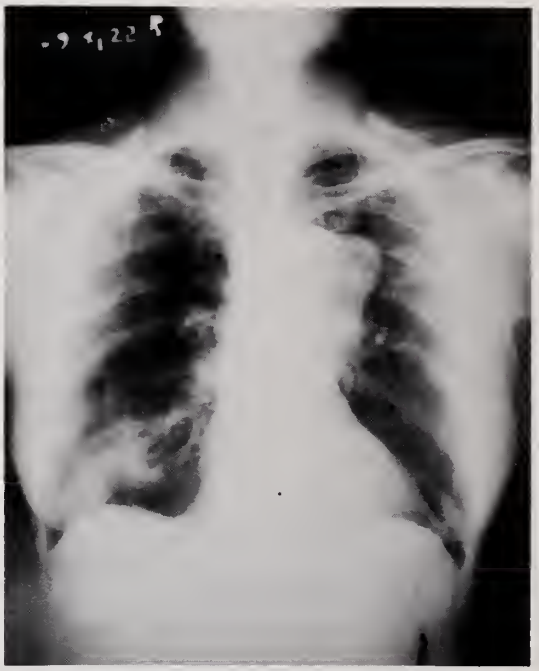


Fig. 4: Pneumonic infiltrate in right base. There is coincidentally an aortic aneurysm.

Chest pain is seen in about 60 percent of patients (15). It is usually pleuritic in character, but in about 10 percent it may be of the anginal type (16). This is the type confused with myocardial infarction. Its pathogenesis has not been clearly established (16).

Another type of chest pain which has not been described in the literature but which we noticed in three patients, was an anginal type of pain aggravated by inspiration. It was precordial, radiating to one or both arms, and of sudden onset. Even though it might had been of pleuritic origin, it did not have the "catching quality"; the intensity of the pain on inspiration was not severe; and no pleural or pleuropericardial rubs were heard. We postulate that this pain is of vascular origin, and related to stretch of the pulmonary arteries caused by increased blood flow to them by inspiration in an already stretched vessel. Stretching of a pulmonary artery has been shown to cause pain (17).

Pulmonary embolism masquerading as asthma was observed in 9 of our patients. Eight had been diagnosed as bronchial asthma and one as cardiac asthma.

The incidence of wheezing in pulmonary embolism has not been previously reported. Sporadic case reports (18) have been published. In the other hand, it has been amply shown that subclinical bronchoconstriction is nearly always present in pulmonary embolism (19).

Of our eight cases masquerading as bronchial asthma, five had a history of bronchial



Fig. 5: Area of increased radiolucency in right mid lung field due to decreased perfussion of such area by a pulmonary embolus. There seems to be increased compensatory blood flow on the left side and probable obliteration of the left costophrenic angle.



Fig. 6: Chest X-ray showing descent of the small fissure, elevation of right diaphragm, and blunting of both costophrenic angles.

asthma. Most of them had been asymtomatic until the time of the embolic episode. It was interesting to notice that in our whole series all patients with history of bronchial asthma manifested wheezing as part of their clinical picture. Item 5 in Table II shows the situations in asthma leading us to suspect pulmonary embolism. One of the team suggested the name "embolic asthma" to differentiate these cases from true bronchial asthma. Webster et al (18) emphasized that their patients had no history of bronchial asthma so as to prove their point that pulmonary embolism per se may cause wheezing. We want to emphasize that patients with history of bronchial asthma suffering pulmonary embolism will exhibit wheezing as part of the clinical picture. It occurred in 100 percent of our cases with history of bronchial asthma.

Why the wheezing in these patients we don't know. It has been shown that patients with history of bronchial asthma are very sensitive to very small amounts of histamine (20), bradykinin (21), slow reactive substance of anaphylaxis (22), etc. The effect of serotonin in humans is not clear. It was proposed by Comroe (23) that serotonin is the substance responsible for bronchoconstriction and vasconstriction on patients with pulmonary embolism. Such serotonin is released from the platelets in the thrombus. We postulate, then, that wheezing is a prominent part of the clinical picture

presented by patients with pulmonary embolic episodes and history of bronchial asthma. The bronchial tree of these patients is sensitized to serotonin, or histamine or whichever substance is responsible for bronchoconstriction in pulmonary embolism. Upon having the episode, the substance is released causing exagerated bronchoconstriction in these patients.

Regarding "cardiac asthma", it is of importance to emphasize that it is not synonimous with paroxysmal nocturnal dyspnea or with acute left ventricular failure unless it is accompanied by wheezing. According to Swineford (24), there are a complexity of factors involving its cause. It is our conviction, too, that cardiac asthma is a syndrome. Our description of one case with congestive heart failure and whcezing precipitated by pulmonary embolism makes us think that an additional etiologic factor of cardiac asthma is pulmonary embolism. The syndrome then includes:

(1) The classical type of cardiac asthma precipitated by acute left ventricular failure.
(2) Thromboembolic asthma or asthma accompanied by right or left heart failure precipitated by pulmonary embolism.
(3) The coincidence in time of atopic bronchial asthma or chronic bronchitis in a patient with heart disease. The clinical picture in these cases might be interpreted as due to congestive heart failure while the true etiology is atopy.
(4) Heart disease with wheezing coinciding, the wheezing related to other miscelaneous types of bronchial obstruction such as tumor, foreign body, etc.

It is our interest to call the attention to the fact that cardiac patients may wheeze because of a multiplicity of factors. We are currently investigating this problem.

Summary

Seventy six cases of pulmonary embolism are presented. The fact that most cases have an atypical clinical picture is emphasized. Eleven (11) percent of cases manifested prominent wheezing as part of the clinical picture. All cases with previous bronchial asthma who suffered pulmonary embolism had wheezing as part of the clinical picture. The major points in the diagnosis of this clinical condition are stressed and discussed.

Resumen

Hemos presentado 76 casos de embolia pulmonar, diagnosticados clínicamente, por autopsia, por arteriografía o cintigrama. Se ha comprobado el hecho de que la mayor parte de los ataques de embolia pulmonar son atípicos y solo es posible el diagnóstico si el médico está consciente de la condición en todo momento. Se enfatiza el hecho de que el 11 porciento de los casos tuvieron sibilancias y cinco fueron diagnosticados originalmente como asma bronquial. Se describen los puntos clínicos de mayor importancia en el diagnóstico de esta condición.

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RADIOISOTOPE SCANNING IN PULMONARY EMBOLIC DISEASE

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Pulmonary embolic disease often mimics other pulmonary and cardiovascular conditions. Its clinical diagnosis is frequently difficult and uncertain. In a great number of cases definite and objective evidence of pulmonary embolism is not obtained with the currently available radiological, electrocardiographic and chemical enzyme studies.

The recent development of an external scintillation scanning technique following the intravenous administration of macroaggregates of radioactive iodine labeled human serum albumin (^{131}I-MAA) affords a new approach to the study of pulmonary blood flow and, consequently, to the study of pulmonary embolism as well as other pulmonary entities.

Lung scanning consists of mapping the distribution of the radioiodine labeled albumin particles temporarily trapped in the precapillary area of the pulmonary parenchyma.

This study presents our clinical experiences with this new diagnostic procedure.

Materials and Methods

Lung scans were performed on fifty-three patients considered to be suffering from various pulmonary and cardiovascular conditions from February, 1967 to October, 1967 at Department of Medicine, San Juan City Hospital.

From the Department of Medicine, San Juan City Hospital, Puerto Rico Medical Center.

On the day of the scanning procedure 0.5 ml of Lugol's solution was given orally to the subjects to block thyroid radioiodine uptake and minimize thyroid irradiation. A total dose of 200 to 300 μc of ^{131}I-MAA was given intravenously with the subject in the supine position. Immediately post injection, scanning was done in the anterior or posterior views or both.

A photo-dot rectilinear scanner with a 5 inches thalium activated sodium iodide crystal was used. Chest X-ray in the anterior, right lateral and left lateral views were done the same day as the scan.

The Normal Lung Scan

In the normal anterior lung scan there is nearly equal distribution of radioactivity throughout both lung fields. The base of the right lung is usually flat, although a decreased concentration of the labeled albumin can be observed at the bases and apices as a result of respiratory excursions. Characteristic areas of decreased activity are well outlined in the regions of the cardiac silhouette and the superior mediastinum (Fig. 1). The cardiac silhouette is less clearly delineated in the posterior lung scan (Fig. 2).

Abnormal lung scans will show one or more areas of decreased activity within the limit of the lung fields corresponding to poorly perfused or non-perfused areas.

Results

Our study includes the lung scans perfor-



Fig. 1: Normal anterior lung scan.



Fig. 2: Normal posterior lung scan.

med in 53 patients throughout an 8 month period. Of these, 25 were found to be suffering from pulmonary embolic disease and 28 from other known clinical conditions.

Positive chest X-rays were obtained in 11 of 25 patients (44 percent) with the clinical diagnosis of pulmonary embolism (Table I). Abnormal scintigraphic findings were observed in 23 of the 25 (92 percent) patients (Table II).

Of the patients with pulmonary embolism, two had a normal lung scan and a normal chest X-ray. Twelve patients had a normal chest X-ray and an abnormal lung scan. Pulmonary arteriography done in two of them confirmed the findings of pulmonary scanning. Four of the patients showed an abnormal chest X-ray with a single affected area and an abnormal single non-perfused area in the lung scan (Table III, IV). Pulmonary arteriography done in three of them confirmed the findings of pulmonary scanning.

In seven cases there were abnormal chest X-rays with multiple non-perfused areas in the scan. Pulmonary arteriography done in two of them corroborated the findings of pulmonary scanning.

The patterns observed in the lung scans of patients with pulmonary embolic disease were as follows:

TABLE I: CHEST X-RAYS IN PULMONARY EMBOLISM

Findings	Number	Per Cent
Negative	14	56
Positive	11	44

TABLE II: PULMONARY SCAN IN PULMONARY EMBOLISM

Findings	Number	Per Cent
Positive	23	92
Negative	2	8

TABLE III: ABNORMALITIES IN LUNG SCANS IN PULMONARY EMBOLISM

Finding	No.
Single non-perfused area	16
Multiple non-perfused area	7

TABLE IV: CORRELATION OF CHEST X-RAY TO LUNG SCAN IN PULMONARY EMBOLISM

X-ray	Scan		No.
Normal	Normal		2
Normal	Abnormal	12	
Abnormal	Abnormal		11
Single defect	Single non-perfused area	4	
Single defect	Multiple non-perfused area	7	

1. decrease or absent of radioactivity in segmental areas, 19 cases
2. crescentic shape filling defects in the periphery, 2 cases
3. diffuse impairment in the concentration of the radioactive material by the entire lung, 2 cases

Single areas of decreased radioactivity were found in 8 patients, and multiple areas in 15.

The distribution of the underperfused areas were as follows: right base in 15 instances; left base in 10; right mid lung in 2; left mid lung in 5; right apex in 5; left apex in 1; whole right lung in 1; whole left lung, in 2 (Table V).

The diagnosis of 28 patients with conditions other than pulmonary embolic disease were: arteriosclerotic heart disease with myocardial infarction or myocardial insufficiency with initial normal electrocardiographic findings, 9; deep thrombophlebitis, 4; hypertensive cardiovascular disease, 2; visceral schistosomiasis with pulmonary hypertension, 2; rheumatic heart disease with intractable failure, 1; pulmonary bullae, 1; pneumothorax, 1; pulmonary abscess, 1; acute pancreatitis, 1; and diabetes mellitus, 1.

Of the above cases, 19 had normal chest X-rays and normal scans, 7 had abnormal chest X-rays and abnormal scans, 1 had a normal chest X-ray and an abnormal scan, and 1 had an abnormal chest X-ray and a normal scan. The last patient had a "coin lesion" 2 cm in diameter, and the lung scan was negative (Table VI).

In the interpretation of the lung scan it is very important to correlate this with other findings including the clinical picture, enzyme studies, radiological studies and arteriography. Of great interest in this respect is the finding of an abnormal lung scan in other conditions besides pulmonary emboli. The findings of non-perfused areas is not specifically diagnostic of pulmonary embolism since many parenchymal lesions are associated with diminished vascularity (1, 2). Clinical conditions that we found to have an abnormal lung scan without pulmonary emboli were: arteriosclerotic heart disease with congestive heart failure, rheumatic heart disease with mitral stenosis and insufficiency, visceral schistosomiasis with pulmonary hypertension, pneumothorax, pulmonary abscess and bronchial asthma with pulmonary bullae.

TABLE V: DISTRIBUTION OF UNDERPERFUSED AREAS IN PULMONARY EMBOLI AND ABNORMAL LUNG SCAN

Area	Right	Left
Base	15	10
Mid-lung	2	5
Apex	5	1
Whole lung	1	2

TABLE VI: PATIENTS WITH CONDITIONS OTHER THAN PULMONARY EMBOLI

Chest X-ray	Scan	No.
Normal	Normal	19
Normal	Abnormal	1
Abnormal	Normal	1
Abnormal	Abnormal	7

Discussion

The pulmonary scan is a safe, innocuous, simple, rapid and effective screening procedure in patients suspected of having pulmonary emboli and can be performed in seriously ill patients without any adverse reactions if material of high specific activity is used (3). No significant hemodynamic, immunologic or radiation hazard has been reported up to the present time.

Since the capillary diameter is approximately seven micra, the pulmonary vessels in the precapillary area trap particles larger than this, with an efficiency of 90 to 95 percent in a single circulation. The diameter of the injected particles ranges from 10 to 50 micra in size. It results in a temporary block in the precapillary area and makes possible the external detection of radioactivity by the scanning technique (4). More radioactivity reaches the normally perfused areas with a consequent striking contrast between the normally and less vascularized areas. The particles are gradually broken down and when their size becomes small enough they are flushed from the lungs by the blood stream with a mean half life of 5 to 10 hours (5). Eventually, they reach the liver where they are removed by the Kupffer cells and metabolized. Within 48 hours, 80 percent of the radioactivity is excreted in the urine when the thyroid gland is blocked (6).

Of the 25 patients with a clinical diagnosis of pulmonary emboli, two had a normal lung scan. This was probably due to a delay in performing the scanning procedure. In 19 patients the lung scan was of great help in the diagnosis of pulmonary embolism. These include the patients with a negative chest X-ray, those who had abnormal but non-diagnostic chest X-rays in whom the lung scan showed multiple non-perfused areas.

In the other 28 patients the scan was done in some because of pathology that could simulate pulmonary embolization such as myocardial disease and in others motivated by the presence of unrelated pathology such as pulmonary hypertension due to schistosomiasis and rheumatic heart disease.

Our observations indicate that the diagnosis of pulmonary emboli can be ruled out when both the chest X-ray and the pulmonary scan are negative. However, there are exceptions to this: 1) when there is a delay in the scanning procedure and, 2) when the emboli are so small that the pulmonary perfusion is not affected. Experimentally, it has been shown

that pulmonary scanning is positive immediately after pulmonary embolic episodes. A pulmonary embolus may be dissolved in 3 to 5 days (7, 8, 9). This is why it it so important to perform the scan as soon as possible after the embolic episode. In our cases, the scanning was done from one to 17 days after the episode, the mean being 4.5 days.

In our experience the presence of a normal chest X-ray and an abnormal lung scan is highly suggestive of pulmonary embolism. Other conditions which can give these findings are pulmonary bullae, acute bronchial asthma and congestive heart failure.

The following cases illustrate some of these experiences.

Case 1:

A twenty-one year old white nurse had a deep thrombophlebitis in left leg five weeks prior to admission. A sudden pleuritic pain in the left side of the chest with palpitations and shortness of breath of one hour duration developed the day prior to admission. On examination she was found to have a blood pressure of 104/70 mmHg, pulse of 102/min., and respiration of 24/min. There were splitting and accentuation of the second heart tone at the pulmonic area. Lungs were clear. There was tachycardia and no heart murmur. The laboratory studies showed a serum lactic dehydrogenase of 875 units and serum glutamic oxaloacetic transaminase of 50 units. The electrocardiogram showed sinus tachycardia. The serum glutanic pyruvic transaminase and the white blood cell count were within normal limits. The chest X-ray was negative. Lung scan showed amputation of both lower lung fields (Figs. 3, 4). Subsequently she had two more episodes of pulmonary emboli which were confirmed by electrocardiograms, serum lactic dehydronases and scans.



Fig. 3: Negative chest X-ray in patient of case 1.



Fig. 4: Lung scanning in case 1 showing decreased perfusion in both lower lung fields.

Case 2:

A twenty-four year old female with history of bronchial asthma during childhood delivered uneventfully a child three months prior to admission. Immediately post-partum she developed intractable asthma. Physical examination was negative except for tachycardia and bilateral diffuse wheezing. Chest X-ray and electrocardiogram were negative. Lung scan showed diminished perfusion in left mid-lung (Fig. 5). Pulmonary arteriography confirmed the presence of a pulmonary bulla in this area.

The following case is representative of the not unfrequent finding of multiple avascular areas in lung scan with a single defect in the chest X-ray in patients with pulmonary emboli.



Fig. 5: Lung scanning in case 2 showing avascular right mid lung in which a pulmonary bleb was demonstrated by pulmonary arteriography.

Case 3:

An 80-year old white male with history of dyspnea, low grade fever and pleuritic left-sided chest pain of one week duration was admitted to San Juan City Hospital on September 8, 1967. Physical examination revealed a blood pressure of 140/80 mmHg, irregular pulse of 110 per minute and respiration of 28 per minute. There were decreased breath sounds in the left lower hemithorax and irregular heart rate of 130 per minute. The liver was palpable one finger below the right lower costal margin. Deep thrombophlebitis in the left calf was found. Laboratory studies showed a lactic dehydronase of 960 units, serum glutamic oxalacetic transaminase of 40 units, total serum bilirubin of 1.5 milligrams percent and indirect bilirubin of 1.2 milligrams percent. Chest X-ray showed an infiltration in the left paracardiac area. The electrocardiogram revealed atrial fibrillation with a rapid ventricular response. The lung scan showed diminished vascularity in left lung and right apex (Fig. 6).



Fig. 6: Lung scanning in case 3 showing avascularity of left lung and right apex.

Summary

The lung scan is an innocuous, safe, easily performed, rapid and effective, screening procedure in the diagnosis of pulmonary embolism. It can be done immediately after the embolic episode in patients seriously ill without morbidity or mortality, if material of high specific activity is used.

Lung scanning was positive in most of (92 percent) 25 cases of pulmonary embolic disease. A negative scan does not rule out

pulmonary embolism. If done late in the disease, it may be negative.

A positive lung scan does not necessarily mean pulmonary embolic disease. The lung scan has to be correlated with the clinical picture, and chest X-ray. The findings are not specifically diagnostic of pulmonary embolism since many pulmonary parenchymal lesions are associated with diminished vascularity (7, 8).

When having a negative chest X-ray with a positive scan, or a positive chest X-ray with multiple areas of decreased perfusion in the scan with a clinical picture suggestive of pulmonary emboli, this is the most likely diagnosis. It is in these situations that lung scanning has its greatest value.

Resumen

El cintigrama pulmonar es una prueba inocua, fácil de hacer y de gran valor en el diagnóstico de embolia pulmonar. Puede hacerse inmediatamente después del episodio embólico, aun en pacientes criticamente enfermos, con muy baja mortalidad y morbilidad si se usa material de radioactividad específica alta.

La prueba fue positiva en el 92 porciento de nuestros casos estudiados con la ayuda de este procedimiento. Sin embargo cabe enfatizar que una prueba negativa, especialmente si se hace tardíamente, no elimina la posibilidad de que haya ocurrido una embolia pulmonar.

No todos los cintigramas pulmonares positivos son diagnóstico de embolia pulmonar. Esta es una prueba más que tiene que correlacionarse en el cuadro clínico y otros estudios. Lesiones tales como bulas, pulmonías y otras lesiones parenquimatosas o vasculares pueden dar un resultado anormal.

Cuando se obtiene una placa de pecho negativa con un cintigrama anormal, o una placa de pecho positiva con áreas múltiples avasculares, el diagnóstico de embolia pulmonar es muy probable. Es en estas situaciones que el cintigrama pulmonar tiene su mayor valor.

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PULMONARY ANGIOGRAPHY

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In 1964 Sasahara and his co-workers (1) described the successful use of selective pulmonary angiography in 8 of 11 patients in whom the diagnosis of thromboembolic disease was suspected. They reported five of their cases in detail. Since then, several other investigators have reported their experience in the use of this technique (2, 3, 4, 5). During the last year the Angiography Team of the Department of Medicine at the San Juan City Hospital has performed 27 selective pulmonary angiograms in 26 patients. Twenty five of these studies were done on patients suspected of having had pulmonary embolism. We will report on our experience with these 25 cases.

Materials and Methods

All studies were performed at the Radiology Department of the Puerto Rico Medical Center with the assistance of members of the department. The following procedure was used. The patients were kept fasting for 5-12 hours prior to the procedure and then taken by stretcher from the ward to the Radiology Department (Fig. 1). Usually no premedication was given. Electrocardiographic monitoring was used throughout the procedure. A D. C. defibrillator, an anesthesia machine and intubating instruments were immediately available. Operating room procedure was followed for scrubbing and draping and a small incision was made over a branch of the median basilic vein at the ante-cubital fossa. A number 7 or number 8 angiographic catheter was advanced under image intensifier control until the tip was at the main pulmonary artery. Five to eight ml of 75 percent Hypaque® was injected to verify the position of the tip and to test for sensitivity to the dye. The table top was then moved until the patient was positioned over a Franklin seriograph and 30-50 ml 75 percent Hypaque® was injected with an Amplatz® power injector at 200-250 lbs/in. The seriograph was programmed to take four per second for 2 seconds and two films per second for an additional 4 seconds, a total of six seconds.



Fig. 1: Angiographic team performing a pulmonary angiogram. Note image intensifier, cardioverter with electrocardiographic monitor and power injector.

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Presented in part at the Annual Meeting of the Puerto Rico Medical Association, November 1967.

Results

Of the 25 studies performed in patients with suspected embolism 5 were of sub-optimal quality and will be discarded for the purposes of this report. The other 20 studies were of excellent radiological quality. The average age of the patients was 51 years. There were 14 females and 6 males.



Fig. 2: Pulmonary angiogram on 46-year old woman with recurrent thrombophlebitis, pleuritic chest pain, pleural rub and rales at the right base, an accentuated second component of the second sound, negative chest X-ray film and LDH of 980 units. There is cut-off of RLL vessels.

Ten arteriograms were interpreted as showing pulmonary emboli, in an additional five the findings were less clear cut and they were labelled as "questionable". Five arteriograms were negative. In the 10 positive arteriograms the average time between admission, or onset of symptoms if the patient was hospitalized, and the study was 5 days with a range of 0-13 days. In the questionable arteriograms the average interval was 13 days and in the negative it was 12 days.

It is now well known that lysis of the embolized clot begins within hours and may be completed, or the clot may fragment and move peripherally, in the first few days after embolization, so that, the sooner the arteriogram is performed, the better the possibilities are that one may demonstrate the embolus. One of the five negative studies was in a patient who had a clearcut pulmonary embolus on clinical grounds but the study was performed 21 days after admission to the hospital.

In 10 patients both pulmonary angiograms and pulmonary scanning were performed. There was correlation between the scan and the arteriogram in all but one case. In two patients both studies were normal. In six, pulmonary emboli were demonstrated in segments corresponding to the scan abnormality. In one an unsuspected bulla was found. In the one case where there was no correlation, a patient with mitral valve disease and congestive heart failure, the normal arteriogram was taken 9 days after the lung scan revealed decreased uptake in the lower left lung.

There has been no mortality and, aside from an occasional premature beat during the catheterization or the injection, no other observable side effect.

Discussion

Pulmonary arteriography is, potentially, the most sensitive and most specific test currently available in establishing the diagnosis of pulmonary embolism. Even at post mortem examinations the use of post mortem arteriographic studies increases markedly the frequency with which this diagnosis is made (6). Arteriography also allows visual quantification of the degrec of vascular obstruction. It is technically an





Fig. 3: Films taken at 1, 2, 3, 4 and 5 seconds after injection showing delay in filling of right lower lobe arterial branches with a negative filling defect proximal to the bifurcation (arrow). There is also segmental oligemia in the posterior basal segment of the left lower lobe.



Fig. 4: Negative filling defect at left pulmonary artery and segmental oligemia in various portions of the lung. An apparent fibrous web is seen at the right pulmonary artery.

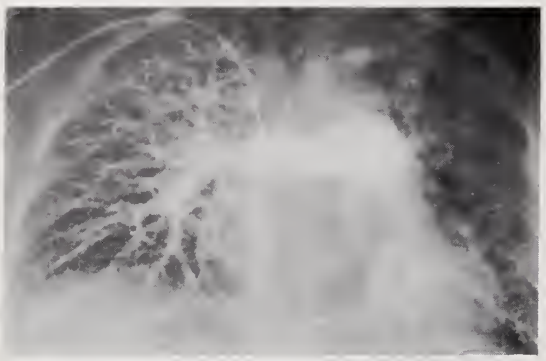


Fig. 5: Marked decrease in blood flow to the left lung in a 22-year old woman with recurrent pulmonary emboli.





Fig. 6: Negative filling defects (arrows) in patients with pulmonary embolic disease.

easy test to perform provided adequate facilities and trained personnel are available. It is a safe test even in severely ill patients. Arteriography and pulmonary scanning are complementary, not competitive, tests. The pulmonary scan is the best screening test for arteriography and only under unusual circumstances should an arteriogram be needed in a patient with an entirely normal scan. On the other hand, pulmonary scanning is relatively non-specific-- other diseases give abnormal scans, it does not give precise anatomic information -- so that, in a patient with an abnormal scan, arteriography should be seriously considered. When acute or chronic embolic occlusion is of such magnitude that surgical intervention is contemplated, or when clinical diagnostic difficulties arise, angiography, in our opinion and in the opinion of others, is mandatory (7). The potential risk of angiography in patients suspected of massive embolism are greatly exceeded by the risk of inappropriate therapy in cases in which the diagnosis is not certain.

The only absolute contraindication for angiography is known allergy to contrast media. Relative contraindications are the presence of ventricular irritability and suspicion of recent myocardial infarction (8). With its prompt, careful and selective use in patients suspected of having pulmonary embolism and with a positive lung scan, it will allow us to make objective diagnosis, establish appropriate therapy and enable us to understand better this frequent yet elusive disease.

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MEDICAL MANAGEMENT OF PULMONARY THROMBOEMBOLISM

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Pulmonary embolization has been recognized as a very frequent occurrence in hospitalized patients (1). Its early and adequate treatment are of paramount importance to the well being of the patients affected. Today we have adequate means for diagnosis and treatment of this rather elusive disease. Intensive research is going on in multiple centers in the world in order to find out better measures to deal with it. It is the purpose of this communication to discuss the medical management of this condition.

The treatment of pulmonary embolism can be subdivided into two main facets, one is surgical and the other medical. Both the surgical and medical measures can be subdivided into prophylactic and specific.

Prophylactic Medical Measures

Among the measures included in this category are avoidance of prolonged confinement to bed, adequate treatment of congestive heart failure, gentle leg exercises and treatment of chronic vein insufficiency of the lower extremities (1, 3). Some clinicians recommend the use of elastic bandages on patients who have to remain in bed for a prolonged period of time. Whether or not their use prevents embolism is controversial. We do not use them in our hospitalized patients. At least in one condition, varicose veins, they might be of some help; in this condition, their use may avoid the development of edema and stagnation which might eventually end up in thrombophlebitis, phlebothrombosis and subsequent pulmonary embolizations. Patients that have suffered a phlebitis should use elastic stockings and avoid prolonged standing, bending of the legs and trauma, especially for the ensuing 5-6 months after the episode. The same applies to the patient who suffers from venous insufficiency of the lower extremities. The patient with extensive varicose veins must not use elastics to hold-up their stockings.

Any patient who is to remain in bed for a long time should get out of bed and walk for a few minutes each day. This simple measure will enhance venous emptying of the legs. Furthermore, those that cannot get out of bed, such as patients with acute myocardial infarction or severe congestive heart failure, should be subjected to passive and active exercises of the legs while in bed (2). For this, you only have to instruct the patient or a relative.

There is evidence proving that high risk patients given anticoagulants do not have as high incidence of thromboembolism as those untreated (2, 4). Thomas advocates, for instance, that those patients that are high risk be treated prophylactically. He includes in

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Presented at Annual Convention of the Puerto Rico Medical Association, November 16, 1967.

this group patients who develop an embolus after surgery or childbirth.

Heparin has also its place in the preventive management of pulmonary embolism. As such it is used in cases of acute myocardial infarction, congestive heart failure and shock (4).

Anticoagulants seem to have a definite place in the prevention of thromboembolic disease in the bed-ridden patient but must be used with caution (2, 4). Smith, Dexter and Dammin (1) in autopsy studies at the Peter Bent Brigham Hospital in Boston found "pulmonary embolism to be the single most common cause of death" in patients with fractures of the hip (9). Many others have reported pulmonary embolism as a very frequent cause of death in patients with fractures of the hip (6, 7, 8, 9). In a controlled study Sevitt and Gallagher (6) demonstrated that prophylactic anticoagulation with heparin or coumarin derivatives can be used effectively to prevent pulmonary embolism. Since then several investigators have used this regime and found it useful.

Specific Treatment

The specific measures include, above all, adequate anticoagulation with heparin (2, 4). Heparin has been used subcutaneously and intravenously. In the acute situation, we prefer to use it via the intravenous route. We follow anticoagulation with the Lee-White clotting time in the absence of a better test. Baseline clotting time is done and repeated in two and four hours. Subsequently, the clotting time is repeated at least weekly since several of our patients who initially were well anticoagulated were subsequently found to be either over or under the desired level. With heparin some people aim to keep the clotting time at 2-3 times the control. We like to keep the clotting time near 15-20 minutes at the fourth hour after the last dose. Our starting dose ranges from 75-100 mg, depending on the size of the patient, etc. Thereafter, the dosage is adjusted according to the response obtained.

A generally accepted concept is that after embolization, at least 4-6 weeks of treatment are a requisite; with heparin at the beginning and later on with coumarin derivatives (9).

We like to keep those patients who have either recurrent phlebitis or pulmonary embolism on coumarin prophylaxis for 6 months to a year at least (2). Several of our patients have had two or more episodes of phlebitis and clinical embolizations. Wagner reported the follow up of patients with pulmonary embolisms with serial scannings of the lungs and was able to demonstrate changes of vascular compromise 4-5 months after the last episode (2). All of the above is evidence in favor of the fact that although many patients get resolution of the clot in a few weeks; some have changes that persist for 4-5 months and need more prolonged anticoagulation. If possible, these patients could be followed with serial lung scanning.

The presence of hemoptysis, unless massive, should not constitute a contraindication for heparinization (9). Most of the time, anticoagulation will prevent recurrences. If there is a recurrence the possibility of inferior vena cava ligation should be entertained. The main contraindications for anticoagulant therapy are bleeding tendency, severe hepatic insufficiency and severe renal insufficiency (3). Notwithstanding, these constitute relative contraindications; heparin, for instance, can be given in the presence of any of the above mentioned complications or a combination of them provided adequate follow up is carried out.

The value of the fibrinolytic agents has been a controversial issue. Recently, much has been talked about urokinase. There is evidence suggestive that it might be of great

help in the future, if wnat has been said regarding this agent, is confirmed. For instance, Sherry et al of the National Institute of Health have reported good or excellent results with urokinase in 40 percent of 39 patients treated (4). Sasahara and others reported short series of patients treated with this agent in whom they obtained good results (10, 11, 16, 20, 21). Nevertheless, it is too early to predict how useful it might result. At the present time, it is generally believed that its clinical use is not justified until further studies confirm its value.

Several factors have been demonstrated to affect the state of anticoagulation, especially with the coumarin derivatives. First, the elderly seem to require less of the anticoagulant than those of the younger age group (15). Second, males require more than females. Third, those who have undergone surgery recently are more sensitive to anticoagulation than those who have not. Fourth, patients with underlying liver disease, such as cirrhosis or hepatitis are also more sensitive. Fifth, the pregnant woman requires more heparin than those that are not pregnant and many prefer not to use the coumarin derivatives in them because they traverse the placental barrier. Lastly, a group of drugs in common usage may potentiate or inhibit the degree of anticoagulation (19).

The first group of drugs to be considered include certain agents that have been found to increase the synthesis of drug-metabolizing enzymes (12, 13, 14, 15), and therefore patients given such drugs require a higher dose of anticoagulants. In this category we include phenobarbital and its derivatives, phehyramidol, griseofulvin and chloral hydrate (17).

The second group to be considered are those related to vitamin K_1. Occasionally, broad spectrum antibiotics may so supress the intestinal flora as to alter the amount of vitamin K absorption and less anticoagulant is needed.

Many other drugs have been reported to influence the degree of anticoagulation. Among them are phenylbutazone and chlofibrate (Atromid®) (18). Probably many more will appear in the future. The lesson we have learned is that any patient on coumadin prophylaxis who is given any other therapeutic agent should be carefully followed up taking in consideration what is already known in relation to the potentiation and inhibition properties of the anticoagulants by other agents.

Summary

We have presented a review of the current concepts of medical management of pulmonary embolic disease. Emphasis has been given to the prophylactic measures and the use of heparin. Up to the present, heparin continues to be the mainstay in the acute treatment of this condition and in the future urokinase could probably become part of our armamentarium.

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SURGICAL ASPECTS OF PULMONARY EMBOLISM

Efraín A. Defendini, MD
Jorge O. Just Viera, MD

Pulmonary embolectomy is truly a 20th century operation. In April 21, 1908, Trendelenburg presented his operation to the German Surgical Congress and demonstrated the operative technique on a corpse. His patient lived for 37 hours postoperatively and died from hemorrhage from an internal mammary artery. It was not until 1924, however, that Kirschner (1) successfully performed pulmonary embolectomy and his patient was exhibited perfectly well 5 years after operation. Trendelenburg was present in the audience when Kirschner reported his successful case, and lived to see a gratifying application of his concepts. It wasn't until Gibbon developed the heart lung machine that embolectomy of the pulmonary artery gained true prominence. Interestingly, cardiopulmonary bypass was developed by Gibbon because of his interest in pulmonary embolism. With successful application of bypass techniques to this problem in the early 1960's first by Sharpe (2) and then Cooley (3) renewed interest in pulmonary embolism has developed.

The initial triumphant reports of removal of multiple large clots from moribund patients, with subsequent survival, made remarkable presentations at medical meetings but have yielded presently to growing controversy as to the precise indications for this procedure. Newer diagnostic techniques, such as pulmonary angiography, radioisotope lung scanning and lactic acid dehydrogenase isosyme determinations have facilitated the diagnosis and study of pulmonary embolism. Experimental and clinical evidence suggest that with time, pulmonary vessels obstructed by emboli may recanalize with restitution of a lumen. In some patients, death occurs before recanalization develops; in others, the embolized vessels remain occluded and pulmonary perfusion may be affected adversely. How to determine what treatment is indicated for different degrees of pulmonary embolism remains a problem.

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Correlation of Clinical and Experimental Findings

Review of our clinical and experimental experience in this field has helped to establish useful guidelines. The clinical records of 103 patients with pulmonary embolism seen from 1949 to 1963 were examined. Of these, 44 patients died and 22 came to autopsy. It is difficult to quantitate the role of pulmonary embolism in these deaths but the mortality certainly remains impressive. Of the patients who died, approximately two-thirds did so within 48 hours of the embolic event.

During the past few years pulmonary embolism has been simulated experimentally by the injection of radiopaque clots. Correlation between the dose of clot injected with lethality was possible. Lethality was associated

with prompt decrease in arterial blood pressure to levels lower than one half baseline, cyanosis, with an arterial oxygen desaturation of less than 70 percent and electrocardiographic changes of myocardial ischemia.

An attempt was then made during review of hospital records to determine whether or not pulmonary embolism in humans was characterized by changes similar to those noted experimentally. Of the 103 patients treated for pulmonary embolism, pleuritic pain occurred in 11 percent, dyspnea in 38 percent, haemotysis in 16 percent and non-pleuritic pain in 35 percent. These signs and symptoms could not be correlated with an eventual fatal outcome.

When the appearance of shock and cyanosis was correlated with lethality, however, an interesting relationship was noted. For example, of the patients who came to autopsy with proven pulmonary embolism, shock had developed sometime before death in 95 percent and cyanosis in 73 percent.

In addition, massive experimental embolism produced shock associated with acidosis, anoxemia, hypercarbia and lactic acid accumulation; a combination of factors which may be lethal even if the blood pressure returns to normal. There is room for a plea that these parameters be measured in patients with pulmonary embolism and therapy directed to correct any deficits demonstrated by such measurements.

The If and When of Pulmonary Embolectomy

Surgical intervention in the improving and asymptomatic patient is debatable. If, however, shock, cyanosis or anginal pain have occurred at any time during the patient's hospital course, strong consideration should be given to pulmonary embolectomy, especially when the patient maintains a compensated cardiopulmonary physiology consistent with survival. If blood gas studies and hemodynamic determinations confirm an inadequate tissue perfusion, there is strong experimental and clinical evidence to indicate that in such a situation the burden of proof and greatest responsibility of the eventual outcome lies on those advising conservative and expectant therapy. The longer one waits when embolectomy is indicated, the higher the operative mortality.

Other Surgical Aspects of Pulmonary Embolism

Prophylaxis probably is the most important aspect in thromboembolism. Circulatory stasis in postoperative and chronically ill patients can be improved by elastic stockings, elevation of the foot of the bed 10 to 15 degrees, early ambulation, and physiotherapy. Clinical dextran appears beneficial in patients with high risk of embolic complications and anticoagulation should also be considered.

Recurrent embolism in properly anticoagulated patients should be treated by venous interruption, either by ligation or plication of the inferior vena. There are patients who in spite of an adequate program of heparinization continue to throw off emboli, and emergency caval ligation is essential in these patients. Procastination may result in death.

Although an occasional patient will be saved by a properly executed and planned pulmonary embolectomy, there is no doubt that the vast majority of patients will benefit from a prophylactic program defined to prevent or minimize the formation of a readily detachable thrombus.

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COMENTARIO:

ACHALASIA AND CARCINOMA: FOOD FOR THOUGHT

Jorge O. Just Viera, MD
Efraín A. Defendini, MD

Thomas Willis first treated achalasia and reported it in 1679. His patient, in danger of death from hunger, was treated by the then Sidley Professor of Oxford, with an "instrument like a rod, of a Whale Bone, with a little round Button Sponge fixed to the top of it; the sick man having taken down meat and drink into his throat, presently putting this down in the esophagus, he did thrust down into the ventricle, its orifice being open, the food which otherwise would have come back again....." Dilatations maintained this man alive for at least 15 years.

But time has passed, fortunately, and what was adequate for Dr. Willis and his patient may not be optimal treatment today. Achalasia is a benign disease compatible with a long life, but the complications commonly found late in this illness often cause disability and even death. The majority of these patients fail to achieve their normal life expectancy especially if the disease begins early in life. Ellis studied the natural history of achalasia in a group of 69 patients and found that 50 percent of the deaths could be attributed to their esophageal disease or its treatment. The incidence of carcinoma was 19 percent for the entire group. Considerable delay took place before the diagnosis of the tumors was established and all were extensive and irremovable.

Because of the high incidence of esophageal cancer in Puerto Rico, every effort should be made to prevent it when possible. Since 1931, thanks to Rake's studies, it has been known that in achalasia acute esophagitis results from stagnation and progresses to chronic esophagitis which in turn eventually results in malignancy.

What symptoms, then, constitute guide posts leading to the diagnosis of carcinoma superimposed on achalasia? Several can be listed, *none pathognomonic:* weight loss, return of dysphagia or change in its character, arrest of swallowed food, cough, regurgitation, anemia, osteoarthropathy, foul odor. Some of these occur in achalasia from the beginning but when they appear anew the clinician should suspect the development of a carcinoma.

A review of the Western World literature pertaining to achalasia and carcinoma was completed recently by one of us. Esophagograms were performed in 57 patients with achalasia complicated by carcinoma and revealed carcinoma in 68 percent. Esophagoscopy had a diagnostic accuracy of 74 percent. Performance of these examinations in patients with long standing achalasia, together with adequate cytologic examination of esophageal secretions, reflect a modern practice of medicine and should yield a high accuracy in detecting underlying carcinoma in achalasia.

The need for treatment of carcinoma as-

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sociated with achalasia suggests failure of adequate treatment of the achalasia itself. What constitutes adequate treatment of achalasia remains a moot question. Since the known natural course of this disease includes an early symptomatic stage which undergoes a deceptive remission, the claims of attained improvement from conservative therapy consisting of drugs or dilatations should be reevaluated critically. The prime goal in the treatment of achalasia remains the provision for adequate drainage of esophageal contents, abolition of stasis, and prevention of esophagitis, not solely symptomatic relief. *Although dilatations achieve excellent symptomatic results in many patients, they will not prevent esophageal dilatation and modification in the wall secondary to stasis. The treatment of choice at present is a Heller operation in which the hypertrophied muscle is divided in its totality without causing esophageal reflux.* If the operation is not done adequately reflux esophagitis will result eventually and prove to be a formidable complication. Esophagogastric myotomy is a safe surgical procedure and can be done with minimal trauma to the delicate sphincter area, making it a more accurate procedure than forcible dilatation. It allows also correction of any other abnormality in the area such as a hiatal hernia or an underlying esophageal carcinoma which may have not been detected.

Adequately done, the Heller operation should be successful in nearly 95 percent of patients. It is hoped that the early performance of a Heller operation will contribute not only to the prevention of carcinoma but also to the diminution of the late complications encountered in patients with achalasia.

EDITORIALES

PROGRESS IN CARDIOVASCULAR DISEASES

During this past decade there has been a truly remarkable advance in knowledge, diagnostic methodology and treatment of cardiovascular diseases.

Knowledge has advanced in the fields of myocardial metabolism and energetics in ischemia and angina pectoris, newer histochemical and electron microscopic technics have aided in the study of cardiac physiology in the normal myocardium and in various myocardiopathies. There has been progress in vectorcardiography and computer analysis, storage and transmission of electrocardiograms. The renin-angiotensin-aldosterone system has been studied extensively and its role in regulating arterial pressure in health and disease has been clarified considerably.

Diagnosis has been more accurate by advances in cardiac catheterization and angiographic technics, including transseptal and retrograde left heart catheterization, left ventriculography and selective coronary cineangiography. Pulmonary scanning technics and pulmonary angiography in embolism and infarction have added some measure of diagnostic precision where it was badly needed. Notable advances in diagnostic enzymology and ultrasoundcardiography have occurred.

Improved technics in cardiopulmonary bypass and open heart surgery have allowed the surgeon to repair a great variety of congenital and acquired defects of the heart and great vessels. The experience with valve prostheses, homografts and heterografts in surgical valve replacement has been extended and many improvements introduced. Myocardial revascularization surgery has received new impetus with the visual scrutiny of results afforded by cineangiography.

Coronary care units have made their appearance and have gained wide acceptance throughout the world. They have been the logical outgrowth of a series of advances beginning with the popularization of closed chest cardiac massage, the effective electrical defibrillation of the heart and the development of oscilloscope monitors of cardiac rhythm with alarm systems, memory loops and automatic recording devices. The high incidence of arrhythmias in the early stages of acute myocardial infarction has been established and the effectiveness of anti-arrhythmic agents has been tested more critically under these circumstances. Electrical defibrillation of the heart and cardioversion of arrhythmias have

become day to day realities in such units. The importance of prompt treatment of bradycardia, tachycardia or arrhythmias to prevent the onset of circulatory arrest has been learned and applied. Cardiac pacemakers have been used widely in the treatment of transient or permanent AV nodal block.

Drug therapy has improved with the introduction of rapidly acting and more potent diuretics, potent antihypertensive agents, a useful beta adrenergic blocking agent and more effective cholesterol lowering compounds.

Cardiac transplantation has been performed serving to point out the strides in surgical technics and the difficulties of suppressing immunological responses. It may serve to stimulate the future development of a self sustained, synthetic, inert organ for temporary pump assistance in post operative states or in cardiogenic shock or for permanent replacement of the severely damaged heart.

All these advances have in no small way increased the already excessive cost of medical services. It will require the sincere cooperation of government, civic organizations, the medical profession and the individual citizen to solve the economic problems brought by advances in technology and its consequent demand for specialization.

J. Fernández Martínez, MD

NUESTRA PROPIA IMPRENTA

Nuestros lectores pueden haber notado el cambio. El número de julio del Boletín fue el primero impreso con nuestro propio equipo. Por iniciativa de nuestro Secretario de Redacción, y con el esfuerzo combinado del personal técnico, la Junta Editora y la Directiva, se ha logrado este paso adelante en la producción del Boletín.

Nuevas técnicas tipográficas permiten la producción de una impresión de buena calidad mediante el uso de equipo cuyo costo es razonable.

Además del beneficio económico en que esperamos redunde la producción del Boletín en nuestra propia casa, será posible resolver otros problemas del pasado tales como el de los atrasos y permitirá mayor flexibilidad y latitud a la Junta Editora en la planificación y composición de cada número.

Julio V. Rivera, MD

ACTUALIDADES MEDICAS

EFFECT OF MALNUTRITION ON MENTAL DEVELOPMENT AND PERFORMANCE

THE LARGER IMPORTANCE OF NUTRITION is beginning to emerge from among its obvious roles of satisfying hunger and promoting physical growth. Present day statistics estimate that approximately two thirds of the children (300,000,000) in the world are undernourished and have some degree of retardation of growth as a result of their nutritional deficiencies.

Recently, studies from developing countries including Uganda, Nigeria, Mexico, Guatemala, Peru, Indonesia, Taiwan and the Philippines have indicated that undernutrition affects the mental development and performance of children. Central nervous system symptoms (irritability, poor performance, etc.) were first reported in children as part of their clinical syndrome of severe protein-caloric malnutrition (kwashiorkor and marasmus). Later, psychological tests for ability were given to chronically undernourished youngsters and showed that they performed at a lower level than those who had been well-nourished.

When Brain Growth Occurs

Interestingly, the newborns in some of the developing countries exhibited superior abilities on neurological examination in contrast to the level of activity seen in babies from Europe and the United States. However, within a year, their performance scores had begun to decrease and eventually reached levels that were some 10 percent to 25 percent lower than normal. These changes were particularly evident in children who had experienced early and prolonged malnutrition. These observations have been interpreted as reflecting mental changes resulting from retardation of normal brain development (i.e., smaller head circumference, and brain mass, etc.) during the first three years of life when more than 80 percent of total brain growth usually occurs.

While the performance levels of these children indicates retardation, this does not imply that they are "mental retardates" — a term signifying deficits of 50 percent to 75 percent and more. As a matter of fact, the capabilities of these children are generally adequate for coping with the limited demands of the society within which they live. However, if their status is to be significantly improved over the long term, they must more fully realize their potential abilities to meet their own needs, as well as to sustain their nations' progress.

Nutrition in a Complex of Factors

Separating malnutrition as a factor in the complex of real life environmental conditions (sociological, cultural, educational, medical) affecting brain function has proved to be extremely difficult. However, ingenuity in scientific design and the invaluable contribution of

statistical analysis have made this manageable.

No single test can provide all of the necessary information, but "composites" of selected techniques give satisfactory results. Nutritional status is measured scientifically through a complete physical examination, physical measurements, X-ray studies of bone growth and biochemical tests on body fluids. Evaluation of mental status has been most satisfactorily accomplished by adopting previous tests such as (Gesell, Cattell, and Wechsler-Bellevue, etc.) In contrast, however with measuring intelligence in terms of the "IQ", the present method measures the individual's performance relative to expected "normal" progress over a period of time. The tests are designed to be "culture-free" and with minor modifications permit comparisons among populations from different parts of the world.

Development of Embryo and Fetus

One thing we know already is that the malnourished mother tends to produce a smaller newborn. The new techniques for measuring cellular structure and composition are now being used to study growth and development during intrauterine life with fascinating discoveries. Information on cell size, numbers and chemical content of the placenta is just accumulating. It indicates that there is a marked reduction in certain components of placentas from malnourished pregnancies compared with those with adequate nutrition. Therefore, the baby may already have been deprived in utero of nutrients necessary for the normal development (differentiation and integrity) of its rapidly growing brain. This may well cause irreversible changes in mental ability.

As for the normal adult brain, it is relatively stable in the presence of malnutrition. Any temporary loss in its activity can be restored with an adequate diet, but where malnutrition during early life is prevalent, the cellular changes that it produces from conception on are never completely corrected. Limitations of mental performance are therefore maintained and perpetuated into succeeding generations.

David Baird Coursin, MD

Reprinted from Unicef News, United Nations Children's Fund — United Nations New York, Issue 53, May 1968.

Study says IUD Safe, Comparable to Pill in Effectiveness

A study involving 3,800 women by the Dade County (Florida) Health Department, Miami, has found the double coil intra-uterine device a safe means of contraception "comparable in use—effectiveness to oral contraceptives."

Drs. Betty J. Vaughn and Hernán Domínguez reported to the sixth annual meeting of the American Association of Planned Parenthood Physicians at the Gunter Hotel, San Antonio, Texas, that the double coil device "could prove to be a valuable addition to the contraceptive methods available to private practitioners." They called it "the contraceptive device of choice for patients with low motivation such as the indigent segment of the population we deal with in our clinics."

Dr. Vaughn is director of the department's maternal and infant care project, with which Dr. Domínguez is also associated. The device used in their study was the Saf-T-Coil, manufactured for Julius Schmid, Inc., New York by Deseret Pharmaceutical Company. The study covered one and a half years.

They said that the double coil device gained acceptance of physicians and public health nurses for three reasons: it comes in a sterilized package that makes unnecessary a sterilizing

procedure at the clinic; it is inserted with greater ease than other intra-uterine devices, and the insertion technique is easily learned by clinic personnel. The Food and Drug Administration's Advisory Committee on Obstetrics and Gynecology, in a January 1968 report (the Hellman report) on intra-uterine devices, emphasized the need for sterility precautions and said that "where sterility packaging is practiced, the bacteriologic controls and checks seem adequate."

A previous attempt in Dade County to use an earlier intra-uterine device, the loop, met with little success, according to Drs. Vaughn and Domínguez, because of professional resistance caused by its being difficult and time-consuming to sterilize and insert as well as being painful to some patients. They reported that during the third quarter of 1966, only 82 loop devices were inserted. The double coil was then introduced and during the next three months, 562 were inserted.

Dr. Vaughn and Domínguez said that patient acceptance of the double coil device reflected professional acceptance and was aided by a booklet explaining the device to patients.

They included in their report a detailed study over a year's period of the first 476 women to use the device.

Of these women, only 14 percent failed to return for examination as contrasted to 57 percent of their clinic's patients on oral contraceptives who failed to return for follow-up. This bears out experience in four New York City clinic groups recently reported by Dr. Hans Lehfeldt, assistant professor of obstetrics and gynecology at New York University. He said that human or psychological factors, seem to be operative in reducing the effectiveness of oral contraceptives to the level attained by intra-uterine device users.

Of the 401 women using the double coil device who were followed up in the Dade County study, only six (1.4 percent) became pregnant. The Hellman report to the FDA considers a pregnancy rate of from 1.5 to 3 percent to be successful.

NOTICIAS

CAMARA DE DELEGADOS

Resumen de las resoluciones aprobadas por la Cámara de Delegados de la AMPR en su reunión del 6 de julio de 1968 en Mayaguez, Puerto Rico.

1. "Enmienda al Reglamento, Artículo X, Sección I, Sociedad de Distrito - Adición".

Aprobada. Por esta resolución la Sección 1 del Artículo X de nuestro Reglamento lee de la siguiente forma: "La Asociación Médica de Puerto Rico estará dividida en sociedades de distrito que contarán de un mínimo de cien miembros agrupados por pueblos en áreas geográficas reconocidas por la Cámara de Delegados. Disponiéndose que cuando se cuente con un número de sesenta médicos asociados interesados en la formación de una Sociedad de Distrito, la Cámara de Delegados podrá autorizar la formación de una Sociedad, dándosele un término de tres (3) años para aumentar su matrícula a cien miembros".

2. "Para solicitar Legislación que Reglamente el Uso de Vehículos de Dos Ruedas".

Aprobada y referida al Consejo de Política Pública para implementación e informe a esta Cámara.

3. "Para Enmendar el Reglamento de la AMPR, Artículo III, Sección 3, Delegados".

Presentada, debidamente considerada y referida al Consejo Judicial y Administrativo para estudio e informe a esta Cámara.

4. "Para Enmendar el Reglamento de la AMPR, Artículo X, Sección 3, Funcionarios".

Presentada, debidamente considerada y referida al Consejo Judicial y Administrativo para estudio e informe a esta Cámara.

5. "Enmiendas al Reglamento de la Sección de Medicina Interna de la AMPR".

Aprobada.

6. "Sobre Implementación de Procedimientos Eticos en la Facultad Médica Activa del Hospital Auxilio Mutuo"

Aprobada con la siguiente enmienda: En el Por tanto punto segundo se añade después de "12 de septiembre de 1968" la frase "quedará sujeto a las disposiciones que establece nuestro Reglamento en su Artículo I, Parte C, Sección 3, Disciplinas". Los siguientes médicos se opusieron a la resolución por no haber suficiente consulta legal: Luis Izquierdo Mora, Carlos E. Bertrán, Alfred L. Axtmayer, Alvarez de Choudens, Martín Iguina, César Rosa Febles y A. L. Rodríguez Rosado.

7. "La Práctica de la Quiropráctica".

Aprobada y referida a la Junta de Directores para su implementación e informe en la próxima reunión de la Cámara.

8. "Para Recomendar el Establecimiento de Cursos Nocturnos de Administración de Servicios de Salud para Médicos en la Escuela de Medicina de la U.P.R.".

Aprobada y referida al Consejo de Educación Médica para implementación e informe en la reunión de la Cámara de Delegados de noviembre.

9. "Para instruir al Comité de Etica a designar normas que controlen la publicación en diarios, revistas y otros medios de comunicación de nombres y fotografías de médicos, así como de la clase médica."

Aprobada y referida al Comité de Etica para

estudio, implementación e informe a esta Cámara.

10. "Para felicitar al Distrito Occidental por la magnífica labor realizada durante todos los actos de la Convención Semianual de 1968".

Aprobada por unanimidad.

PROGRAMA DE SALUD

A continuación reproducimos el "Programa de Salud" aprobado por la Cámara de Delegados de la AMPR en su reunión del 6 de julio de 1968 en la ciudad de Mayaguez:

"Los pacientes deben recibir la más alta calidad de servicios de salud, independientemente de su condición social, económica, raza, creencias políticas y religiosas.

Favorecemos programas encaminados a estimular la formación de nuevos médicos tanto generalistas como especialistas y de personal auxiliar.

Se respetará y defenderá de toda supeditación política la libertad e independencia profesional de los médicos y auxiliares.

Recomendamos la aportación de incentivos a los ciudadanos, para que de acuerdo con los recursos y con la aportación gubernamental, puedan acogerse a seguros médico-hospitalarios voluntarios prepagados globales con libre selección de médico y hospital.

Favorecemos la construcción y remodelación de facilidades hospitalarias de todo tipo dándole incentivos a los hospitales de la comunidad y privados.

Recomendamos la creación de un Departamento de Salud Mental y de una Junta Estatal de Salud.

Nos reafirmamos en nuestra campaña de combatir los problemas médico-sociales tales como la adicción a drogas, alcoholismo, prostitución y enfermedades venéreas.

Seguiremos ayudando en la prevención, rehabilitación y en la creación de facilidades para el retardado mental.

Recomendamos la progresiva ampliación y mejoramiento del sistema de asistencia pública, programas de comedores escolares, estaciones de leche y distribución de alimentos.

También recomendamos se aprueben las medidas necesarias para que se aumente la ayuda directa a los beneficiarios del programa de Bienestar Público fomentando la rehabilitación de éstos en casos que sea factible.

Insistimos en la ampliación de los programas de saneamiento ambiental incluyendo infestaciones parasitarias, inmunizaciones, control de vectores, contaminación del aire, cuerpos de agua, tanto en su fase de purificación como de depuración.

Recomendamos la ampliación de los programas contra las enfermedades crónicas degenerativas y ocupacionales.

Cooperaremos con las agrupaciones cívicas y de la comunidad que bregan con los problemas de salud estimulando un esfuerzo común entre la ciudadanía y el gobierno en la solución de los problemas de salud.

Estamos conscientes que no podrá tener éxito algún programa de salud sin la debida educación y orientación de la comunidad la cual consideramos de fundamental importancia".

ACTIVIDADES

Sep. 7 - 3:00 p.m. - Reunión Sub-Distrito Núm. 1 del Distrito Sur - Club de Leones de Guayama. *7:00 p.m.* - Buffet-Baile.

Sep. 10-11 - AMA Speakers Program Seminar in cooperation with P. R. Medical Association - Hotel Puerto Rico Sheraton.

Sep. 21-- 8:00 p.m. - Homenaje Dr. Fernando Cabrera - Hotel San Juan - Salón Isla Verde.

Sep. 30 a Oct. 4 - 8:00 p.m. - Cursillo Post Graduado de Ortopedia y Traumatología - Anfiteatro Hospital Municipal de San Juan en el Centro Médico. El 4 de octubre en la Casa del Médico - Ponce, P. R.

Nov. 12-16 - Sexagésima Sexta Convención Anual de la AMPR - Hotel San Juan - San Juan, P. R.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

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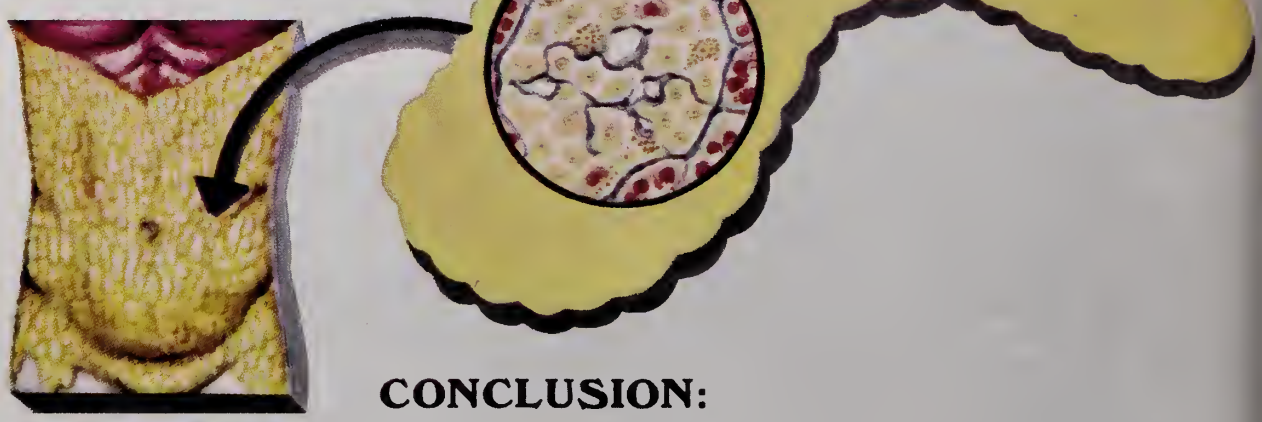
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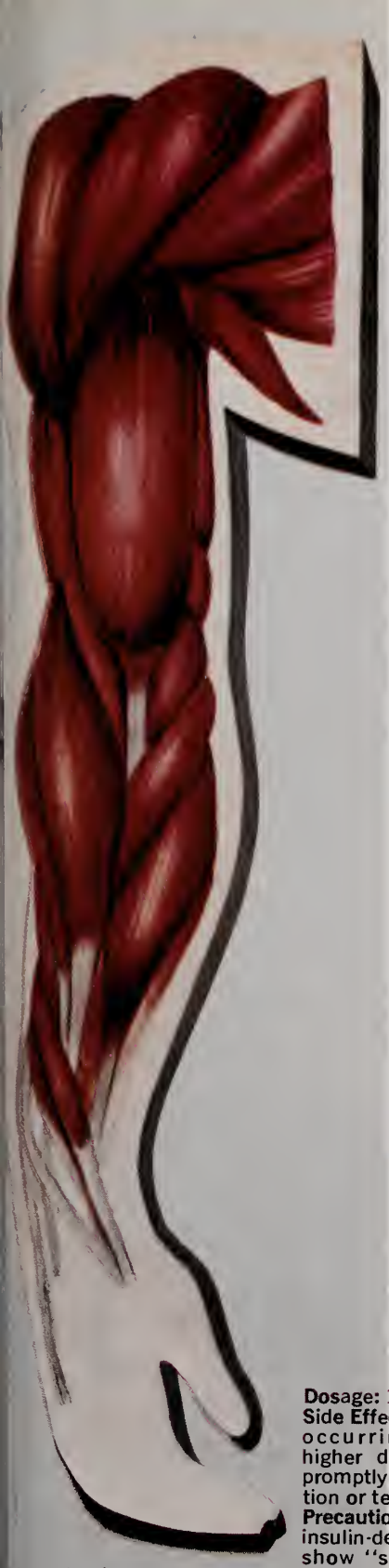
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DBI-TD, on the other hand, acts independently of the pancreas to promote increased glucose utilization in skeletal muscle.[6,7] DBI-TD increases the entry of glucose into muscle cells, possibly by facilitating the action of insulin on muscle; it does not increase glucose uptake by the fat cells or prevent them from releasing fatty acids and glycerol. Thus, in the overweight stable adult diabetic who often releases excessive endogenous insulin in response to hyperglycemia, DBI-TD supplements the insulin action and may compensate for its physiologic inefficiency in this regard.[4,6,7]



CONCLUSION:

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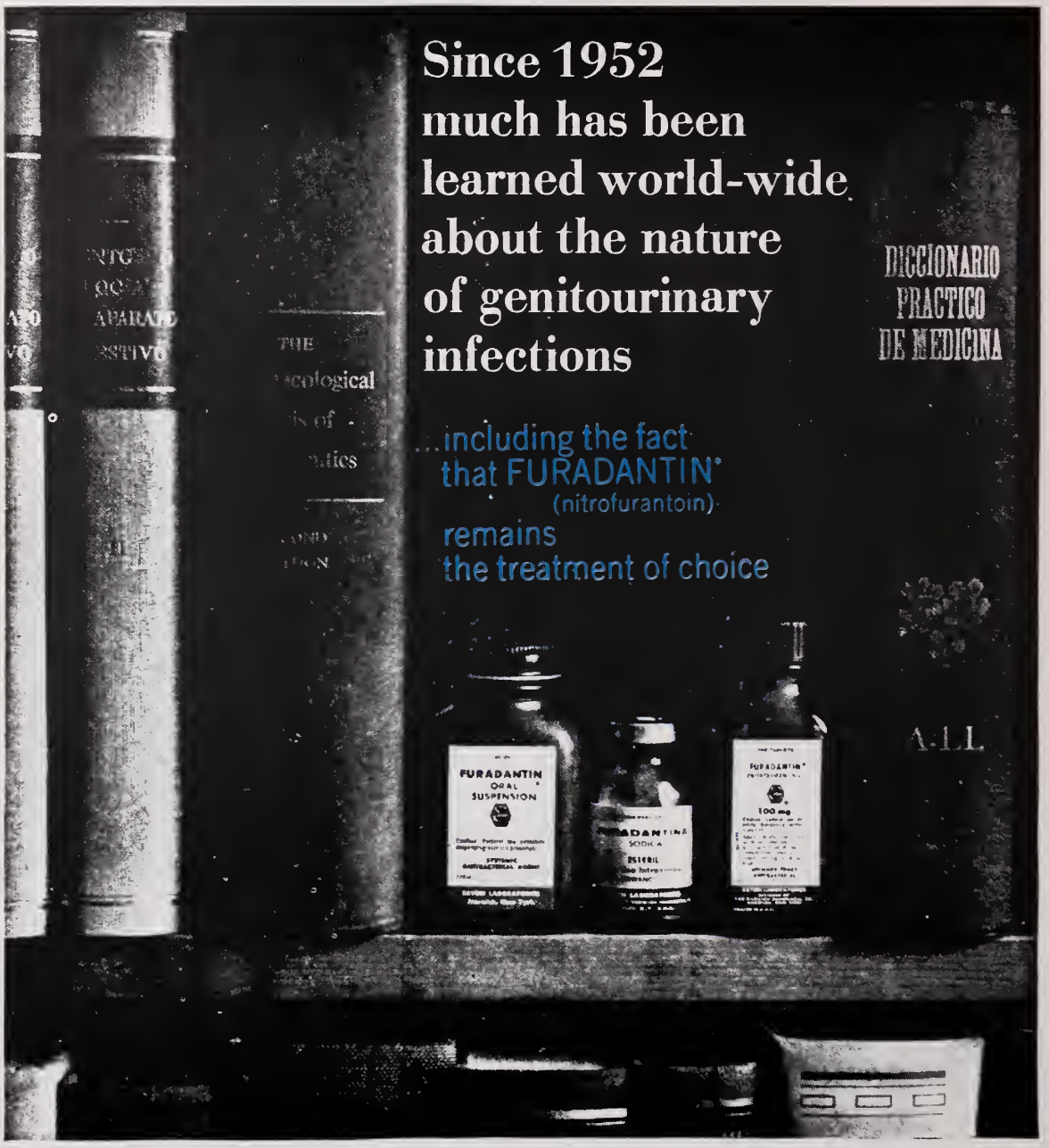
- Lowers blood sugar
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*Although anorexia has been suggested as a possible basis for weight loss, controlled studies do not support this. In nondiabetic subjects who are overweight, comparable doses of DBI-TD do not induce weight loss or lower blood sugar.

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References: 1. Yalow, R.S. and Berson, S.A.: Diabetes 9:254, 1960. 2. Grodsky, G.M. et al.: Metabolism 12:278, 1963. 3. Gundersen, K. and Antoniades, H.: Proc. Soc. Exp. Biol. Med. 104:411, 1960. 4. Williams, R.H.: Textbook of Endocrinology, Ed. 3, Philadelphia, Saunders, 1962. 5. Gordon, E.S.: Advances Internal Med. 12:66, 1964. 6. Butterfield, W.J.H. and Whichelow, M.J.: Diabetes 11:281, 1962. 7. Searle, G.L. and Cavalieri, R.R.: Presented at 26th Ann. Meet. Amer. Diabetes Ass., Chicago, June 25-26, 1966.

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Adverse Reactions: Side effects most commonly reporte drowsiness, fatigue and ataxia. Infrequently encountered: co fusion, constipation, depression, diplopia, dysarthria, headach hypotension, incontinence, jaundice, changes in libido, nause changes in salivation, skin rash, slurred speech, tremor, urinar retention, vertigo and blurred vision. Paradoxical reactio such as acute hyperexcited states, anxiety, hallucinations, i creased muscle spasticity, insomnia, rage, sleep disturbanc and stimulation have been reported; should these occur, use the drug should be discontinued. Because of isolated reports neutropenia and jaundice, periodic blood counts and liv function tests are advisable during long-term therapy. Min changes in EEG patterns (low-voltage fast activity) observe during and after therapy and are of no known significance.

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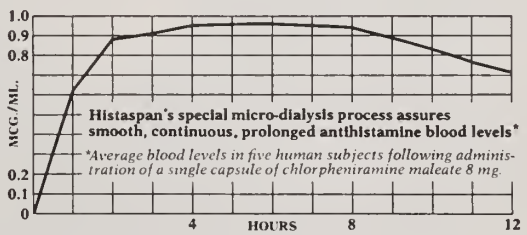
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Histaspan protects when the patient is most active. Exertion that produces even mild fatigue seems to aggravate pollinosis symptoms. Moreover, functional changes in the G.I. tract during vigorous activity may alter the rate of release of most other antihistamines, resulting in erratic and perhaps inadequate blood levels. Since its release is unaffected by G.I. function, Histaspan maintains therapeutic blood levels even when the patient is most active.



Indications: *For symptomatic relief of allergic manifestations in vasomotor rhinitis, hay fever, urticaria, angioneurotic edema, sensitivity reactions, insect bites, other itching skin conditions including pruritus ani, pruritus vulvae, pruritus of drug rashes, atopic dermatitis and contact dermatitis.* **Contraindication:** *Known hypersensitivity to the drug.* **Precautions:** *Since drowsiness or dizziness may occur, patients should be cautioned about driving or operating machinery.* **Side Effects:** *May include drowsiness, dizziness, dry mouth, disturbed coordination, blurred vision, G.I. disturbance, tachycardia, headache, nervousness, weakness, and urinary disturbances.* **Dosage:** *For both the 8 mg. and 12 mg. strengths: adults and children over age 12, one capsule in the morning, and one at night (q. 12 h.).* **How Supplied:** *Capsules—two strengths: 8 mg. and 12 mg. chlorpheniramine maleate; bottles of 100.*

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Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institut countermeasures if the white count chang significantly, granulocytes decrease, or in mature forms appear. Use greater care in elderly and in hypertensives.
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latent peptic ulcer. The patient should instructed to take doses immediately after ea or with milk to minimize gastric upset. urash occasionally occurs. If it does, otly discontinue the drug. Agranulocyto si exfoliative dermatitis, Stevens-Johnson nome, Lyell's syndrome (toxic necrotiz- idermolysis) or a generalized allergic ac on similar to a serum sickness syn- e may occur and require permanent th awal of medication. Agranulocytosis n ccur suddenly in spite of regular, re- ad normal white counts. Stomatitis, sali- yland enlargement, vomiting, vertigo and or may occur. Leukemia and leukemoid ac ons have been reported. While not defi- el attributable to the drug, a causal rela- n ip cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity, angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily. In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and other factors influencing drug response. Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

For complete details, please see full Prescribing Information.

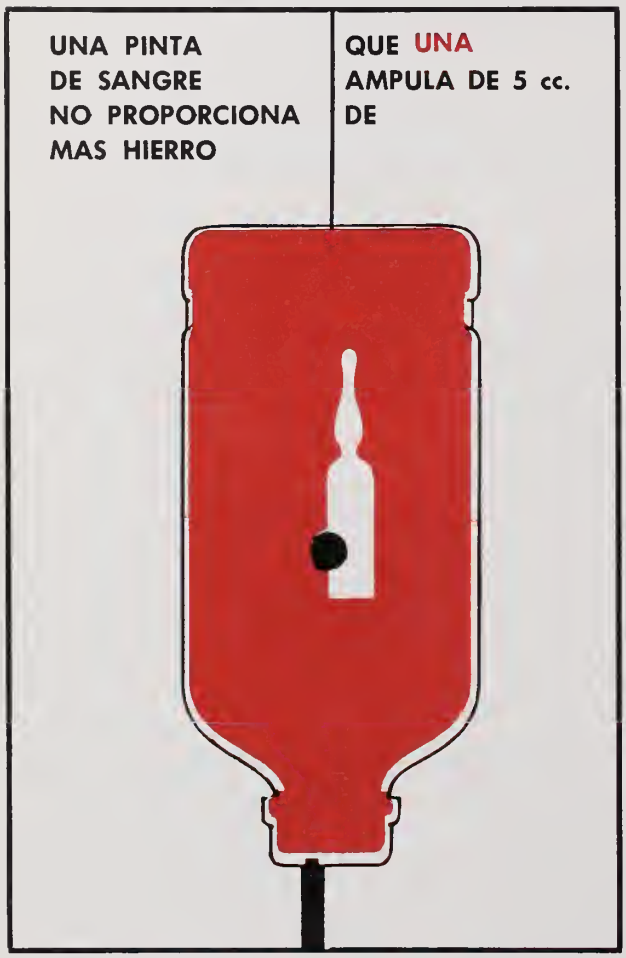
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(B) 46-800-A

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

TA-5806AR

Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

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PARA PACIENTES
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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

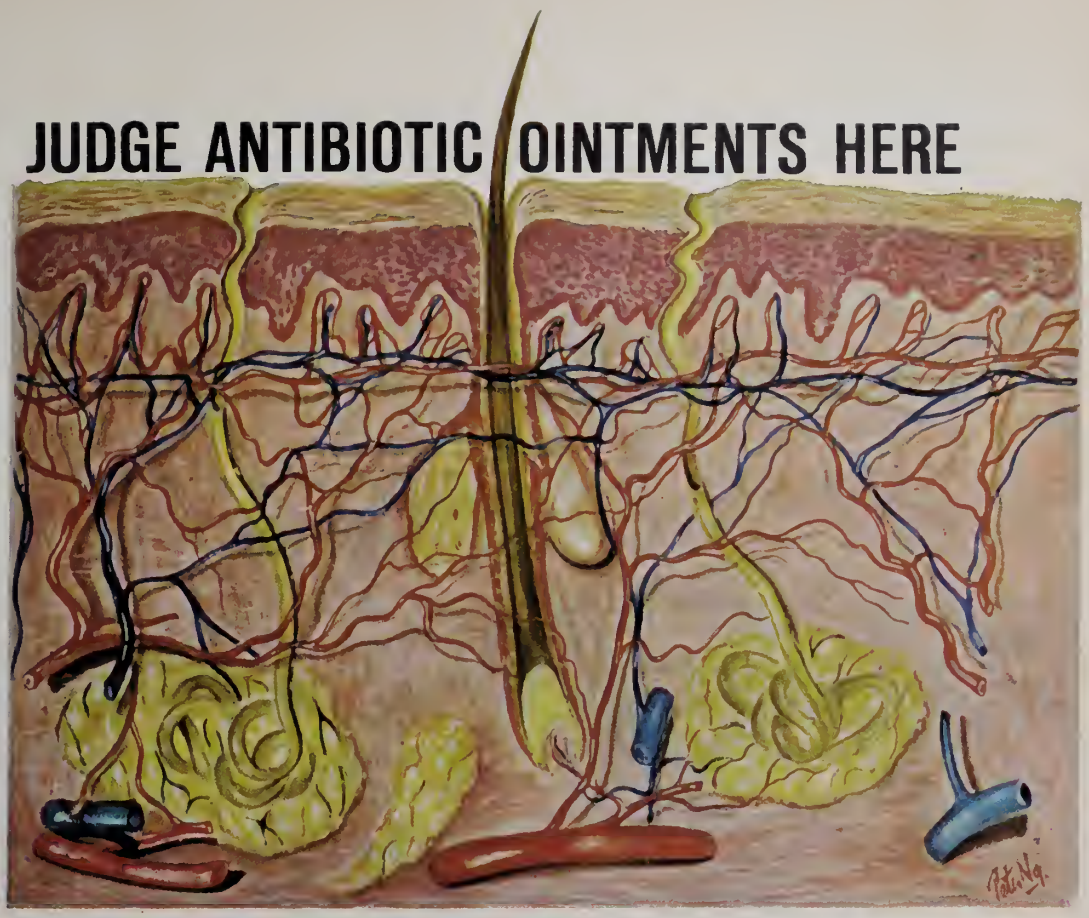
EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patient should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



Dosage in Painful Shoulder: Initial: 3 to 6 capsules daily in 3 or 4 equal doses. Trial period: 1 week. Maintenance dosage should not exceed 4 capsules daily; response is often achieved with 1 or 2 capsules daily.

In selecting the appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response. (B)R 46-070-A

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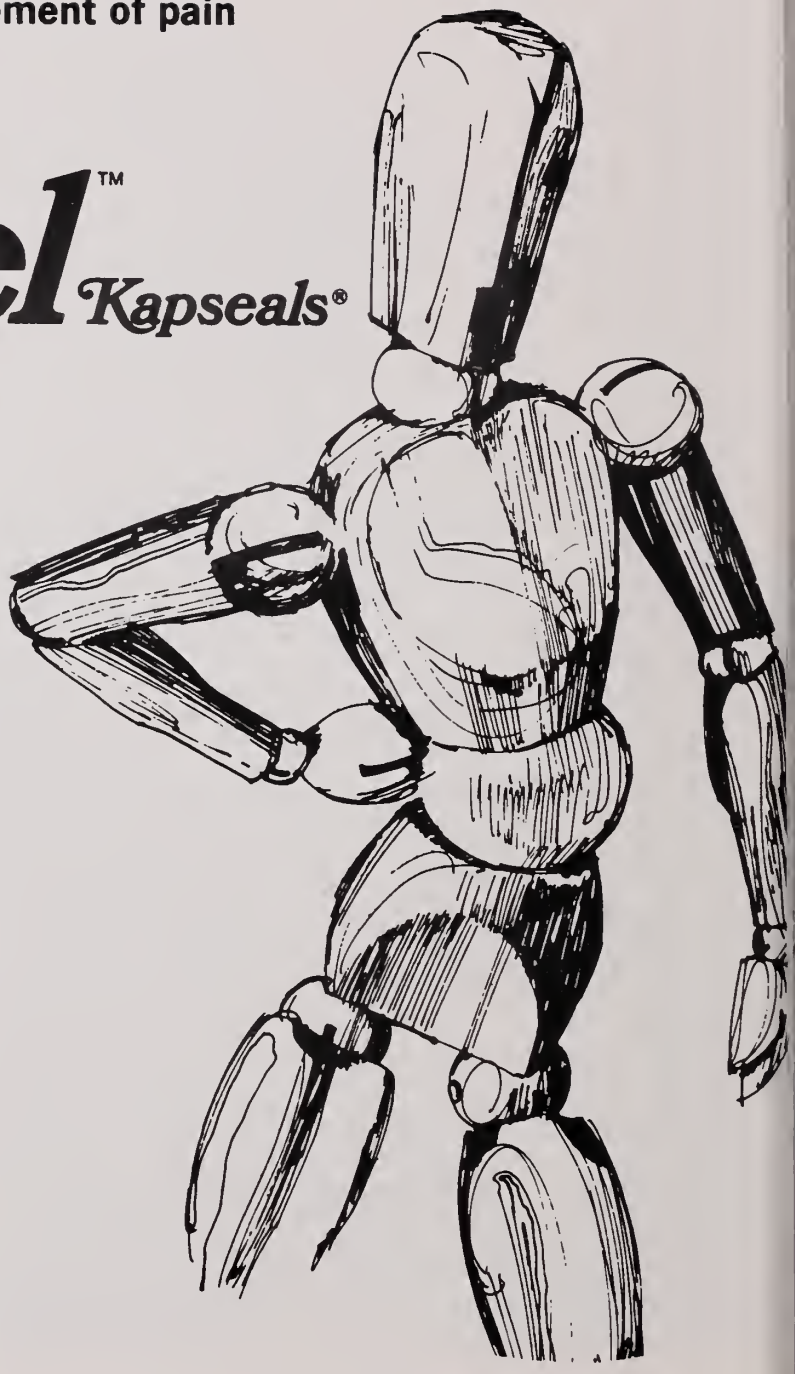
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El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

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SIFILIS:
Evaluación de las Pruebas Serológicas

V. M. Torres Rodríguez, MD

En 1952, cuando comencé mis labores de médico general en el Centro de Salud de Añasco, tuve que bregar, entre muchas otras cosas, con un número considerable de pacientes supuestamente sifilíticos que habían sido tratados en repetidas ocasiones con "cursos de penicilina" y para quienes parecía no haber más remedio que seguir tratándose, pues su serología permanecía positiva. También se acostumbraba diagnosticar y tratar de primera intención como sifilítica, a cualquier persona cuya sangre resultase "positiva". Nos cuestionábamos en aquel entonces la sabiduría de estas decisiones pues habíamos sido debidamente aleccionados en nuestros años de estudiante sobre la persistencia de la positividad en algunos sifilíticos, no importando el tratamiento más adecuado del mundo, y la existencia innegable de serologías falso-positivas. Nos esforzábamos por esclarecer estos problemas, pero el peso del trabajo y lo apremiante del tiempo, y la duda de la cual no puede escapar el generalista que no tiene consultoría accesible, obligaban en más de las veces al camino más corto y fácil, el tratar con penicilina a unos y otros. Catorce años más tarde nos dispusimos a la tarea de la enseñanza especializada a residentes de Dermatología y descubrimos que todavía imperaban las mismas prácticas y las mismas dudas en la mente del no-sifilógo. Esto, a pesar del tremendo progreso que ha habido en las técnicas y el desarrollo de las pruebas serológicas.

Es nuestro propósito en esta ocasión discutir el estado actual de este importante capítulo de la medicina.

De la División de Dermatología, Departamento de Medicina, Escuela de Medicina de Puerto Rico y Hospital Universitario.

Presentado ante la Asamblea Anual del Distrito Este, Asociación Médica de Puerto Rico, Enero 1968.

Historia

Desde el 1906, en que Wasserman, Neisser y Bruck publicaron su prueba serológica (1), un año después que Shaudinn y Hoffman descubrieron el *Treponema pallidum* como causante de la sífilis (2), el diagnóstico de esta enfermedad dejó de ser puramente clínico. Las pruebas de sangre, que desde entonces utilizan como antígenos substancias no-específicas, vinieron a ser imprescindibles, pero esa falta de especialidad daba lugar a reacciones positivas en estados no sifilíticos. Sólo indicaban la presencia de reagina, un anticuerpo que se encuentra en la fracción globulínica de las proteínas séricas y que se desarrolla durante infecciones causadas por varios gérmenes, entre ellos el de la sífilis, además de otras enfermedades no infecciosas y en algunos individuos aparentemente normales. La búsqueda de una prueba en que la positividad indicara que en efecto el paciente tenía o había tenido sífilis culminó en 1949 cuan-

do Nelson y Mayer publicaron su trabajo sobre la inmovilización por suero sifilítico de treponemas virulentas — *Treponema pallidum* immobilization (TPI) test (3). El antígeno es ya, no extractos del corazón de la res, sino la espiroqueta misma. Estimulados por el hallazgo de Nelson y Mayer, y tratando de obviar las dificultades y el alto costo inherentes en el TPI, varios investigadores se lanzaron en pos de otras técnicas, unas usando el treponema intacto, vivo o muerto, otras usando espiroquetas no-patógenas que comparten estructuras antigénicas con el treponema sifilítico, y aún otras basadas en fracciones químicas de estos microorganismos. La aplicación, publicada por Deacon *et al* en 1957 (4), del procedimiento de fluorescencia indirecta de anticuerpos a la serología de sífilis abrió un capítulo que nos trae hasta el presente con la prueba de anticuerpos treponémicos fluorescentes en la que se eliminan del suero, mediante absorción antigénica, los anticuerpos no-específicos para el *Treponema pallidum* – (Fluorescent treponemal antibody absorption) (FTA-ABS) test (5).

Al paso con los adelantos en antígenos treponémicos, aunque parcialmente opacados por la sofisticación e interés de estos, también se ha progresado en las pruebas que usan los no-treponémicos, esto es, variaciones de extractos cardiolípidos, que siguen siendo sumamente valiosas en la evaluación y tratamiento de los pacientes en consideración. Se han ideado pruebas rápidas y sencillas, algunas de las cuales pueden hacerse en pocos minutos, que parecen ser adecuadas, especialmente en la exploración de grandes grupos de personas.

Pruebas Serológicas Tradicionales (No-Treponémicas)

Las pruebas tradicionales son de dos tipos: de fijación de complemento y de floculación o precipitación. En la primera, evolucionada del Wasserman, al mezclar el antígeno con el suero se determina la presencia de anticuerpos si estos, al combinarse con el antígeno, fijan complemento, no dejándolo libre para actuar en un sistema indicador hemolítico presente en el tubo. La ausencia de hemólisis es evidencia de "positividad". Las pruebas de floculación consisten de la formación de cúmulos, visibles por el microscopio regular, al mezclarse el antígeno con el suero en una laminilla. Se hacen diluciones ascendentes del suero, permitiendo así una titulación cuantitativa del mismo. Con el advenimiento de nuevas técnicas y la experiencia adquirida en muchos años se ha concluído que una batería de pruebas no es necesaria en la mayoría de los casos. Se ha demostrado que las pruebas de floculación, que son más fáciles de llevar a cabo, sirven plenamente los propósitos deseados y por lo tanto han suplantado las de fijación de complemento en muchos laboratorios. La que se considera standard hoy día es el VDRL (Prueba de laminilla del Venereal Disease Research Laboratory) y es informada como "Reactiva", "Débilmente Reactiva", o "No-Reactiva". En todos los casos en que es positiva se somete el suero a varias diluciones y se expresa el resultado en "dils", significando esto la más alta dilución en la que el suero fue positivo.

Pruebas Serológicas Rápidas Introducidas en los Ultimos Años

(1) *Rapid Plasma Reagin* (RPR Test), 1957 (6):

Esta prueba economiza tiempo al no tener que calentarse ni coagularse el plasma. Utiliza un antígeno derivado del antígeno básico del VDRL y contiene cardiolípido, lecitina y colesterol, además de cloruro de colina para inhibir las substancias presentes en el plasma frío que intervienen con la agrupación de an-

tígeno-anticuerpo, y etileno dinitrilo ácido tetra-acético, que evita la deterioración del antígeno.

(2) *Plasmacrit Test*, 1962 (7):

Esta es una variante del RPR que utiliza el plasma descartado en las determinaciones de microhematocrito.

(3) *Unheated Serum Reagin Test (USR)*, 1961 (8):

Utiliza suero sin calentar evitando así la media hora de baño caliente del VDRL.

(4) *Rapid Plasma Reagin Card Test*, 1962 (9):

Esta es una prueba que puede hacerse en menos de 10 minutos y no requiere el uso de microscopio, centrífuga, o tubos de ensayo. Se utiliza una tarjeta especial *(Brewer plasma collection card)*, que tiene una depresión similar al roto de la llave de una cerradura. Una gota de sangre se coloca en la parte circular de la depresión, la cual está cubierta por un anticoagulante y una lectina, substancia que ocasiona la agrupación de los eritrocitos y leucocitos. El plasma separado se canaliza hacia la hendidura de la depresión desde donde se transfiere con un tubo capilar graduado a pequeñas depresiones en otra tarjeta plástica. Se añade una gota de antígeno, que es parecido al del RPR Test, pero que contiene carbón coloidal, lo que hace posible una lectura macroscópica. Son positivos aquellos especímenes que muestran amontonamiento de partículas de carbón. Esta prueba tiene una correlación excelente con el VDRL.

Las pruebas no-treponémicas, aunque no específicas para la sífilis, son esenciales y aventajan las que utilizan treponemas o sus productos por las siguientes razones:

(1) por ser más económicas y fáciles son excelentes como prueba inicial, especialmente para *screening;*

(2) confirman el diagnóstico cuando se correlacionan con el historial y la evidencia clínica de sífilis;

(3) su positividad es muy significativa en la evaluación epidemiológica de contactos y sospechosos;

(4) cuando el informe cuantitativo indica un título alto o ascendente son prácticamente diagnósticas de sífilis, aunque se han informado falsos positivos biológicos con títulos altos (10, 11);

(5) en el seguimiento de un bebé en quien se sospecha sífilis congénita las pruebas cuantitativas son valiosísimas;

(6) la respuesta serológica después del tratamiento ayuda a determinar si el tratamiento ha sido adecuado o no;

Por otro lado, según ya se ha mencionado, estas pruebas pueden ser falso-positivas o lo que es igualmente importante, falso negativas. Los estadíos falso-negativos son los siguientes:

(1) en sífilis temprana, la serología es usualmente negativa antes de la quinta semana (y a veces más tarde), desde la exposición, esto es, se suele dar el caso de un chancro seronegativo;

(2) en sífilis congénita de algunas semanas, antes del desarrollo de anticuerpos;

(3) en sífilis congénita tardía, con estigmas, incluyendo queratitis intersticial activa;

(4) en sífilis tardía las pruebas pueden ser negativas en 10 porciento de pacientes con sífilis tardía mucocutánea, ósea, o viseeral, en 20 porciento de pacientes con sífilis cardiovascular y en 33 porciento con tabes dorsalis (12); también pueden ser negativas en sífilis ocular tardía (13);

(5) en el fenómeno de pro-zona.

El fenómeno de pro-zona no es muy bien entendido en el cual, los anticuerpos altamente concentrados en ciertos casos aparentemente apabullan al antígeno, de suerte que en el suero sin diluir la reacción es negativa, pero según se va diluyendo, va apareciendo la positividad. Se dice que esta anormalidad no es tan rara como se cree (14). El peligro

de la misma estriba en que si rutinariamente sólo se prueba el suero concentrado el resultado será "no-reactivo". Es necesario siempre hacer una serie de diluciones para descubrirlo. Para hacer el asunto más complicado se ha informado el fenómeno no sólo en sífilis sino también en un paciente con linfosarcoma que mostraba una reacción falso-positiva en las pruebas de rutina (15).

Hay un grupo de enfermedades y condiciones no-sifilíticas que pueden dar lugar a reacciones positivas, entre ellas las siguientes:

A. Otras treponematosis (frambesia, pinta, bejel). En realidad estas no representan reacciones "falso-positivas" ya que las espiroquetas causantes comparten totalmente la antigenicidad del *Treponema pallidum.*

B. Otras infecciones o infestaciones tales como la lepra, fiebre por mordida de rata, brucelosis, tifo, infecciones respiratorias comunes, mononucleosis infecciosa (aunque no tan frecuentemente como se cree; solamente en 0.66 porciento en contraste con el 20-30 porciento frecuentemente citado) (16); enfermedad de Weil, vacunación contra viruela, linfogranuloma venéreo y malaria.

C. Otras enfermedades tales como el lupus eritematoso, la leucemia, los linfomas y el sindrome de Banti.

D. Estados aparentemente "normales", como en personas jóvenes sin evidencia de enfermedad (algunos pueden tener o desarrollar otras anormalidades séricas y deben ser evaluados para posibilidad de enfermedad seria), y el proceso de envejecimiento (10, 17).

En un estudio planeado para investigar el envejecimiento como causa de reacciones falso-positivas en 71 ancianos comparados con 71 controles jóvenes, Tuffanelli encontró que 19 pacientes mostraron pruebas positivas. En adición, hubo una incidencia significativa de auto-anticuerpos: 31 porciento mostraron anticuerpos antinucleares y 32 porciento el factor reumatoideo y en un número significativo hubo anormalidades en la electroforesis sérica pero no el factor LE ni tiroglobulinas (10).

Thomas, en un excelente monógrafo publicado en 1949, antes de la adopción de la prueba de TPI, en la discusión de los casos falso-positivos de causa desconocida, enfatiza la importancia de un historial adecuado en estos pacientes y clasifica aquellos cuyo historial no sugiere sífilis en la forma siguiente: (1) no hay historial de posibles lesiones tempranas; no ha habido contacto sexual, no hay evidencia de sífilis congénita ni en el historial de paciente ni en el de los padres o hermanos; (2) no hay historial de posibles lesiones tempranas; no ha habido contacto sexual excepto con individuos conocidos que no tienen un historial de sífilis y quienes han sido examinados y encontrados negativos para sífilis, incluyendo una serología negativa. Concluye esa sección diciendo: "Se espera devotamente que pronto tengamos disponibles medios prácticos para distinguir entre pruebas serológicas para sífilis verdaderas y falsas" (18). Poco tiempo después se evaluaba extensamente la prueba de Nelson y Mayer.

Pruebas Serológicas Treponémicas

La prueba inicial, el TPI, depende de la presencia en el suero de un anticuerpo específico que al contacto con la espiroqueta, bajo condiciones especiales, causa su inmobilización. Este anticuerpo se forma más lentamente que la reagina, la prueba siendo negativa en los estadíos tempranos de la enfermedad. En mujeres embarazadas afectadas el anticuerpo pasa a través de la placenta, igual que la reagina, pero persiste en la sangre del infante durante más tiempo que ésta (hasta 7 meses). Tiende a ser relativamente estable al calor, requiere complemento para su acción y aparentemente es treponemicida. Según es de

lento en formarse, así es de persistente una vez establecido, usualmente permaneciendo en la sangre por el resto de la vida del paciente. La prueba consiste en mezclar una suspensión de *Treponema pallidum* virulento, obtenida de sifilomas testiculares del conejo, con el suero del paciente, en presencia de complemento, e incubarla por cierto tiempo. Luego se cuentan las espiroquetas inmobilizadas en un microscopio de campo obscuro y se compara el porcentaje con controles. Por su gran especifidad (98-99 porciento), sigue siendo a manera de una vara de medida para las otras pruebas, pero por su alto costo, la necesidad de técnicas altamente especializados, y la variación en diferentes laboratorios ha sido adoptada por sólo un pequeño grupo de instituciones (19, 20).

Después del TPI surgieron otras pruebas, pero ya por ser igualmente complicadas, sin añadir mucho, como el Treponema Pallidum Immune Adherence (TPIA) (21), y el Treponema Pallidum Agglutination (TPA) (23), Treponema Pallidum Complement Fixation (TPCF) (24), Reiter Complement Fixation (RCF) (25), y el Reiter Protein Complement Fixation (RPCF) (26), estas dos últimas usando extractos proteicos de la cepa de treponemas no-patogénicas Reiter que comparten antigenicidad con el *Treponema pallidum*, todas fueron siendo descartadas gradualmente. El RPCF fue estudiado extensamente en laboratorios de Salud Pública estatales pero se encontró que no era un substituto adecuado para el TPI – había muchas reacciones negativas en los casos en que más se necesitaba una prueba positiva, especialmente en sífilis tardía.

En 1957, Deacon *et al*, publicaron sus hallazgos con la prueba de anticuerpos treponémicos fluorescentes (FTA) (4). En ésta, espiroquetas de la cepa Nichols se secan sobre una laminilla y se cubren con suero. Los anticuerpos específicos presentes (globulinas) cubren los microorganismos los que al ser tratados con antiglobulina humana marcada con fluoresceina brillan al ser examinados en un microscopio de campo obscuro iluminado con luz ultravioleta, ya que la antiglobulina fluorescente reacciona con la globulina previamente adherida a ellos. Si no había globulinas específicas en el suero las espiroquetas no brillan al ser tratados con la antiglobulina. Originalmente se usó una dilución del suero 1:5 pero en ésta, y aun hasta 1:100, se encontraron muchas reacciones no-específicas debidas a anticuerpos hacia otras espiroquetas saprofíticas comunes en el ser humano (*e.g.*, *Treponema microdentium)*. Al diluir el suero 1:200 se logró más especifidad pero se perdió gran parte de la sensibilidad (el FTA – 200) (27). Luego se demostró que podían absorberse del suero los anticuerpos hacia las otras espiroquetas con un extracto hidro-soluble de treponemas no-patógenas Reiter, usado en vez de la salina amortiguadora en la dilución 1:5, dejando solos en esa concentración ventajosa los anticuerpos específicos para el *Treponema pallidum*. Este es el Fluorescent Treponemal Antibody Absorption (FTA-ABS) Test que se usa hoy en día en la gran mayoría de los laboratorios como prueba treponémica para la sífilis en casos especiales (5). Es tan específica como, y ciertamente más sensitiva, que el TPI test. Es usualmente positiva más tempranamente que el VDRL y es excelente para evaluar los supuestos falso-positivos biológicos y los falso-negativos en los casos de sífilis tardía.

Los laboratorios centrales del Departamento de Salud del Estado Libre Asociado llevan a cabo rutinariamente pruebas cuantitativas de VDRL y el FTA-ABS cuando es solicitado por las unidades de Salud Pública, Centros de Salud, o médicos privados.

Recomendaciones en la Evaluación Serológica de Pacientes

Se hacen las siguientes recomendaciones para

la evaluación de la serología en pacientes sospechados de tener sífilis:

(1) Pacientes con lesiones sospechosas, o contactos de casos conocidos cuyo VDRL es positivo se diagnostican como sifilíticos, tomando en consideración el título cuantitativo sólo como ayuda en el seguimiento del caso. Después de un curso de tratamiento adecuado, si el título ha descendido a niveles bajos, no es necesario volver a tratar, aunque se mantenga la serología positiva por un tiempo prolongado. Esto sucede con frecuencia y es proporcional al tiempo que pasó antes de empezar el tratamiento, tendiendo a permanecer positiva indefinidamente en casos tratados más de dos años después de haber comenzado la infección. Una fluctuación de una o dos diluciones usualmente no es significativa pero si hay un aumento considerable en título es posible que haya habido una recaída o una reinfección, en cuyo caso es necesario volver a tratar al paciente. Es imprescindible en estos casos hacer un examen del líquido cefaloraquídeo para determinar la posibilidad de sífilis del sistema nervioso central.

(2) Pacientes con lesiones sospechosas, sean estas tempranas o tardías cuya serología rutinaria es negativa deben ser sometidas a un FTA ABS test, el cual será positivo en los casos sifilíticos. Naturalmente en lesiones tempranas se deben hacer exámenes de campo obscuro, los cuales, si son positivos, eliminan la necesidad de la serología para el diagnóstico inmediato.

(3) Pacientes con serología positiva, por lo general con títulos bajos, pero ocasionalmente altos, en los que no haya sospecha alguna de sífilis y en quienes el historial es negativo, deben someterse a un FTA-ABS test. Si éste es negativo se diagnostica un falso-positivo biológico. Luego se debe evaluar al paciente para otras condiciones que pueden ser más o menos serias. En ancianos es posible que no se encuentre causa obvia alguna. Si el FTA-ABS es positivo debe concluirse que el paciente tiene sífilis latente.

(4) Pacientes con sífilis congénita, ya sea temprana o tardía, generalmente tienen serología positiva. Ahora bien, puede ser negativa bien temprano o en algunos casos en las etapas tardías, y en ellos un FTA-ABS test es de gran ayuda. Se debe recordar que en sífilis congénita en infantes puede ocurrir el fenómeno de pro-zona. Afortunadamente no se ha encontrado este fenómeno en las pruebas treponémicas. Tampoco debe olvidarse que un infante de una madre con serología positiva, aunque ésta haya sido adecuadamente tratada, suele también tener una serología positiva durante los tres primeros meses de vida. ya que la reagina traspasa la barrera de la placenta. En estos casos se sigue al niño con serología cuantitativa, observándose un descenso gradual hasta hacerse negativa en niños no infectados, mientras que en los infectados la serología se mantiene alta o sube de título.

(5) Mujeres embarazadas cuya serología es positiva deben ser cuidadosamente examinadas y cuestionadas sobre serología y embarazos anteriores, especialmente si han terminado en aborto después de los primeros cinco meses, considerándose que la sífilis no afecta al feto antes de este tiempo. Si una mujer ha sido satisfactoriamente tratada previamente no es necesario volver a tratarla si la serología se mantiene baja en repetidas ocasiones y no hay evidencia de una recaída o reinfección. Si pruebas anteriores han sido negativas siempre debe tomársele la serología al marido y si ésta es negativa debe pensarse en un falso-positivo en la esposa. Naturalmente, en casos de duda es necesario someter el suero al FTA-ABS test. Si se sospecha sífilis activa y se confirma con serología positiva debe tratarse la mujer embarazada lo antes posible para beneficio de ella y su criatura y ésta debe ser seguida cuidadosamente después del naci-

miento. Es recomendable examinar la serología varias veces durante el embarazo pues puede suceder que sea negativa al principio pero positiva más tarde.

Es bueno recordar que el diagnóstico de sífilis nunca debe basarse solamente en una prueba positiva. El estigma que el mismo deja y el sufrimiento que ocasiona, amén de las molestias y posibles complicaciones de tratamiento innecesario, son suficientemente serios como para ameritrar más cuidado antes de sellar un paciente con él.

Resumen

Hoy por hoy el médico tiene a su disposición magníficas pruebas serológicas, tanto tradicionales no-treponémicas como las más modernas que usan treponemas como antígenos, para la evaluación cuidadosa del paciente sifilítico y del no-sifilítico en quien algunas de estas son positivas. Se describen las técnicas tradicionales, algunas de las rápidas introducidas en los últimos años, y las específicas, especialmente el FTA-absorption test, el cual se efectúa en el laboratorio central del Departamento de Salud y que es valiosísimo para el esclarecimiento de casos dudosos.

En adición al historial y examen físico clásicos el uso inteligente de estas pruebas nos permite establecer correctamente el diagnóstico, tratamiento y seguimiento de la sífilis, y nos ayuda en otras enfermedades que pueden tener igual o más seriedad. Errores en la apreciación y evaluación de estas pruebas suelen tener consecuencias trágicas.

Summary

At the present time there are excellent serological tests for the evaluation of syphilis and of non-syphilitic patients in whom some of them may be positive. A description is made of the traditional tests, of some of the rapid ones introduced in the last few years, and of the specific ones which utilize treponemes antigens, especially the FTA–absorption test. This test for the clarification of doubtful cases is available at the central laboratory of the Department of Health. In addition to the classical history and physical examination of the patient, the intelligent use of these tests permits the correct diagnosis, treatment, and follow-up of syphilis, and helps in other equally serious diseases. Sad consequences may occur from errors in the appreciation and evaluation of these tests.

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BLOOD GROUPS OF PUERTO RICANS

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The real biological significance of blood group substances is unknown but since their discovery by Landsteiner and Levine in 1900 they have acquired great importance in science. Due to their relation to blood transfusions and hemolytic disease, knowledge about them is an essential part of the practice of medicine. Since they have been found to be inherited as Mendelian characters they have assumed a vital role in genetics, anthropology and forensic medicine. At least 14 different blood group systems are recognized today in man but amongst them the ABO and Rh systems are the most important and the only ones routinely tested for in blood typing.

The irregular distribution of the ABO groups in the world's population is one of the phenomena related to these substances of interest to the biologist and the anthropologist. Some racial groups are characterized by a high incidence of one group or another, for example: some Indian tribes in North America are practically all O group while some Mongol populations have a predominance of B and Australian aborigenes are mostly A. This irregular distribution of some blood groups probably did not occur at random and there are those who believe that blood group prevalences are indicative of a selective influence in evolution (1).

Some evidence has accumulated that there may be a relation between blood groups and some diseases (2). Thus, it may be accepted as a proven fact that pernicious anemia is more common in the group A population and so is carcinoma of the stomach while peptic ulcer is more common among group O non-secretors. Since we have interest in studying possible relationships between some of our tropical diseases and the blood group constitution of our population we needed as a starting point a reliable study of our blood group distribution. As we approached the problem we were soon made aware that surveys of the ABO and Rh(D) incidence in Puerto Ricans had already been published. The earliest study was that of Serra published in 1932 (3) and covering the ABO group. Another study was published in 1945 by Mercedes Vicente de Torregrosa (4) covering both the ABO and RH(D) groups. Nevertheless, we felt that a study based on a larger population sample such as was available to us from the files of the American Red Cross was desirable and would provide a firmer base for conclusions.

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Materials and Methods

Up to the moment of our consultation the files of the American Red Cross in Puerto Rico con-

TABLE I: MALE DONORS

Blood Group	No.	Percent	Total	Percent
O^+	11,277	48.38	12,457	53.44
O-	1,180	5.06		
A^+	7,415	31.81	8,217	35.24
A-	802	3.44		
B^+	1,911	8.20	2,092	8.98
B-	181	0.78		
AB^+	504	2.16	545	2.34
AB-	41	0.18		
Total	23,311	100.01	23,311	100.00

tained organized information on the ABO and Rh(D) types of 30,533 donors. The information is contained in cards with the name of the donor, the site of the blood collection, the age and the sex. There is no information as to the racial extraction of the donor. No donors are accepted below the age of 18 or above 60 years. Male donors outnumber females by a ratio of 3:1. Typing is done from a blood sample obtained at the time of the blood collection by the slide method using commercially available typing antisera. These files were made available to us through the courtesy of Dr. J. R. Becerra. We went through each card tabulating the sex, ABO and Rh(D) types of each donor. The information obtained enabled us to calculate the percentages that are summarized in Tables I, II, III and IV. Since each donor has a single card, no matter the number of donations there is no chance of duplication. We took care to eliminate donors from the Virgin Islands where the Puerto Rico Chapter of the American Red Cross also collects blood. We did not screen the cards to eliminate non-Puerto Rican donors living in Puerto Rico, but it is thought that their number is not significant. The sampling is adequate not only because of the large numbers involved, but because of the modus operandi of the Red Cross that in collecting blood from all the communities of the Island probably satisfies the conditions of a representative sample.

Results and Comments

Tables I, II, III and IV are compilations of the data obtained in the study. It appears that 53.79 percent of Puerto Ricans are O type, while next in frequency is A with 35.06 percent, next is B with 8.83 percent and finally there is AB with 2.32 percent. How these frequencies compare with other nations or racial groups is seen in Table

TABLE II: FEMALE DONORS

Blood Group	No.	Percent	Total	Percent
O^+	3,621	50.14	3,968	54.94
O-	347	4.80		
A^+	2,243	31.06	2,488	34.45
A-	245	3.39		
B^+	561	7.77	603	8.35
B-	42	0.58		
AB^+	144	1.99	163	2.26
AB-	19	0.26		
Total	7,222	99.99	7,222	100.00

TABLE III: MALE AND FEMALE DONORS

Blood Group	No.	Percent	Total	Percent
O^+	14,898	48.79	16,428	53.79
O-	1,527	5.00		
A^+	9,658	31.63	10,705	35.06
A-	1,047	3.43		
B^+	2,472	8.10	2,695	8.83
B-	223	0.73		
AB^+	648	2.12	708	2.32
AB-	60	0.20		
Total	30,533	100.00	30,533	100.00

TABLE IV: Rh INCIDENCE

Sex	Rh^+	Percent	Rh-	Percent
Male	21,107	90.55	2,204	9.45
Female	6,569	90.96	653	9.04
Total	27,676	90.64 *	2,857	9.36 *

Average

TABLE V: ABO DISTRIBUTION IN P. R. AS COMPARED TO OTHER COUNTRIES (6)

	O	A	B	AB
Puerto Rico *	53.8	35.1	8.8	2.3
American Indians (Utah)	97.4	2.6	0	0
Australian Aborigenes	48.1	51.9	0	0
Basques	57.2	41.7	1.1	0
English	47.9	42.4	8.3	1.4
Negroes (USA)	51.5	29.5	15.5	3.5
White (USA)	42.2	39.2	13.5	5.1
Chinese	30.7	25.1	34.2	10.0
Asiatic Indians	32.5	20.0	39.4	8.1

** Present study, not included in reference (6).*

TABLE VI: STUDIES ON THE INCIDENCE OF BLOOD GROUPS IN PUERTO RICO

Study		ABO				Rh(D)	
	No.	*O*	*A*	*B*	*AB*	+	–
Serra (3)	5,135	46.7	29.9	13.5	9.7	–	–
Torregrosa (4)	429	48.7	38.7	9.6	3.0	89.04	10.96
Present	30,533	53.8	35.1	8.8	2.3	90.64	9.36

TABLE VII: Rh(D) DISTRIBUTION IN PUERTO RICO AS COMPARED TO OTHER COUNTRIES (6)

Country	Rh(D) Percent +	
Puerto Rico	90.6	9.4
American Indians	100.0	0.0
Australian aborigenes	98.4	1.7
Basques	69.5	30.6
English	83.4	16.6
Negroes (USA)	95.5	4.5
White (NYC)	86.0	14.0
Chinese	98.6	1.5
Asiatic Indians	90.3	9.7

V. We have a higher incidence of O than both American negroes and whites which may perhaps reflect a small admixture of Indian blood in our veins. The O group incidence in Puerto Rico is also higher than that of the Spanish in whom according to Alvarez (5) the incidence is slightly over 38 percent. Thus neither our Spanish or African patrimony explains our unexpectedly high O blood group incidence and the popular notion that there is considerable Indian blood in Puerto Rican veins receives some support. *

Table VI compares the Rh(D) incidence in Puerto Rico to other nations and racial groups. It appears that our incidence lies somewhere between the incidence in purely white populations such as the English, or New York white, and the Negro. This is well in accordance with the historical make-up of our demography; predominantly European and African.

Finally, in Table VII we compare our figures with those of the two previously published surveys and we find that there are perhaps significant differences in relation to the ABO blood groups but in the case of Rh(D) incidence, Torregrosa's results (2) were essentially equal to ours although her study was based on only 429 cases. We presume that improvements in typing techniques and materials explain the difference between the results of Serra's study and the other two.

Summary

A study of the incidence of blood groups in Puerto Rico has been carried out. For this purpose the files of the American Red Cross, Puerto Rico Chapter, were surveyed. Approximately 30,000 donors were used as a probably representative sample of the population of the island and the results indicate that 53.79 percent of Puerto Ricans are group O, 35.06 percent group A, 8.83 percent group

** This point will be further elaborated on a paper in preparation on Diego factor studies in Puerto Rico.*

B and 2.32 percent group AB. The Rh(D) positive incidence is 90.69 percent.

Resumen

Hemos hecho un estudio de la distribución de los grupos sanguíneos ABO y Rh(D) en la población de Puerto Rico empleando los datos acumulados en los registros de la Cruz Roja Americana de Puerto Rico. El estudio se basa en aproximadamente 30,000 puertorriqueños de ambos sexos entre las edades de 18 y 60 años.

Los resultados indican la siguiente distribución de fenotipos: grupo O, 53.79 porciento; grupo A, 35.06 porciento; grupo B, 8.83 porciento y grupo AB, 2.32 porciento. La incidencia del fenotipo Rh(D) es 90.69 porciento.

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ON PUERTO RICANS:
Folk and Scientific Explanations

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One of the most distinguishing characteristics of man is the psychological capacity for self-objectification, to view himself as a distinct object in a world of other objects. Every human society has developed a set of beliefs and ideas to explain the existence of man, his relationship with nature, and his place in the cosmos. These explanations differ from one society to another due to the fact that the way in which people tend to self-objectify is to a large extent a cultural product. As a consequence the members of a culture tend to share a self-image, and what anthropologists have called a world-view. The world view consists of the way in which members of a culture look at the world; of all their beliefs and explanations about themselves, nature, and other people, as well as their relationship with the unknown or supernatural. With the exception of the fully isolated human groups, such as some bands of Eskimos who at the time of their discovery by Europeans considered themselves to be the only people inhabiting the world, all cultures have developed a set of explanations to account for the physical and cultural differences of the other human groups with whom they have had some contact. Why are these people different from us? — is a question that men have been asking themselves from the moment they saw other human groups with physical and cultural traits different from their own.

These explanations can be divided in two types: folk and scientific. Scientific explanations consist of a body of rules based on facts and derived from them by logical inference. While these rules must be open to control by experiments and/or critique by reason, folk explanations are not subjected to a rigorous process of analysis and critique. The latter tend to be accepted as part of the inherited cultural tradition. Although folk explanations are not necessarily illogical the process of thought by which they are derived is different from the scientific approach. Both types of explanations co-exist in all societies, but, tribal, peasant, and traditional societies depend more on folk theories than does western civilization. In the western world there has been a progressive tendency to develop scientific theories to replace traditional folk explanations of natural and social phenomena. Thus, in our modern secular world, the biblical explanation for the origin of man has been replaced by evolutionary theory, while the folk belief that diseases are caused by spirits is being substituted by explanations based on the findings of laboratory research and modern medicine. However, in many of the prevalent concepts about physical and cultural differences between human groups many folk explanations persist in spite of the development of western scienti-

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fic thought concerning racial and cultural diversity.

The case of the Puerto Ricans in the United States who are classified as a race when compared to Negroes and Whites is an example of the persistence of folk explanations even among highly educated people. Although we do not constitute a race, the fact that we are considered members of a racial minority in the United States is a good example of what I have called a folk conceptualization of racial differences, which classify human groups either as belonging to one of the "pure" races such as the White, Negro, and Yellow races, or as "mixed" races which developed through miscegenation of the pure stocks. On the other hand, the folk explanation of racial differences assumes that national, linguistic, religious, and cultural differences in human groups coincide with racial divisions. Both assumptions are false, as has been extensively demonstrated by anthropologists and geneticists. (Physical Anthropologists and Geneticists - June 1951).

The scientific definition considers that a race is "*a population which differs from other populations in the frequency of some of its genes...*" (Dunn 1959:90). According to Dobzhansky (1962:228), races are "*Mendelian populations which differ in the incidence of some genetic variants in their gene pools.*" Thus, race differences are between populations and not between individuals. The term population is used here in its biological context "*as denoting a group of people who share a common pool of genes through reproductive communication by intermarriage.*" (Dunn 1959:106). The fact that we Puerto Ricans do not constitute a breeding or Mendelian population rules out the possibility of classifying us as a race if we utilize a scientific explanation for racial differences. An example of the genetic diversity in Puerto Rico is that a group can be classified as "Negroes", according to the folk explanation, or as American Coloured according to the scientific explanation. The American Coloured is a population which includes all of the New World Negroes. This population exhibits certain differences in its gene pool (when compared to African Negroes) as a result of the constant gene flow between them and other racial groups since slavery was introduced in America. It should be emphasized that racial differences are differences in the genetic constitution and not necessarily differences in phenotypes or observable physical characteristics. Furthermore, the folk explanation considers that races are static units, while the scientific explanation points out that races are dynamic entities to which the mechanisms of natural selection are applicable. Human populations are always adapting to new environmental situations in a slow and constant process. Hybridization or gene flow is another important mechanism in the process of race formation. An analysis of how both mechanisms are involved in the process of racial differentiation shows that it is not possible to maintain the folk belief in racial purity. Most anthropologists, with the exception of those who have been involved in developing racism and related ideologies, claim that there is no evidence for the existence of pure races. (Dobzhansky 1966:255).

> *The evidence points out that human hybridization has been going on for an indefinite but considerable time. Indeed, one of the processes of race formation and race extinction or absorption is by means of hybridization between races. (Physical Anthropologists and Geneticists – 1951).*

A Puerto Rican is a member of an ethnic or cultural group who can be distinguished from members of other cultural groups by the combination of the following characteristics: (1) he was born or his parents were born in the island of Puerto Rico (in the case of Puerto Ricans living in the United

States descent might have to be traced back to the grandparent's generation); (2) in most cases Puerto Rican Spanish is his vernacular language; (3) he considers himself a Puerto Rican; and (4) he shares a common cultural heritage with other Puerto Ricans.

The third category, to identify himself as a Puerto Rican, and to establish a distinction between who is a Puerto Rican and who is not, is probably the most important because it provides the individual with a cultural and national identity as well as a sense of solidarity with other people he considers to be Puerto Ricans. To define the common cultural heritage is out of the scope of this short paper, but a good discussion of what constitutes the Puerto Rican cultural heritage, and the problems that arise when trying to establish what is a national culture can be found in Steward (1956), and Mintz (1966).

In conclusion, we Puerto Ricans are a national and cultural group, not a race, in the same way that North Americans are not a race, nor the French or the Russians. The folk classification of Puerto Ricans as a race is based on false premises about what constitutes significant racial differences, and it has been established according to certain stereotypes which have created a folk image of how a Puerto Rican looks like. These stereotypes are reinforced by several non-racial traits shared by most Puerto Ricans which consist of cultural and personality traits which distinguish us as a cultural group.

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MOTIVATION

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Before we go into motivation let us review the personality structure of the individual. Let us try to understand why different individuals react differently to similar situations.

Fundamentally, the personality of an individual arises from two sources. What we are born with and develop as we grow up, and what we acquire by coming into contact with the environment. As infants, we want food, love, warmth and comfort. As infants, we want these things immediately and if we don't get them we react by crying. At this time of life we are aware only of ourselves and the desires and cravings of our body.

As we grow older we come to realize that there are others about us who are bigger and stronger. Eventually we realize that in order to get what we want we have to please these powerful figures about us. This process goes on throughout the entire life of the individual.

Agreed upon by the majority of the psychiatrists and psychologists is that the reasons for our actions, whether we are aware of them or not, are determined by one basic principle. We always react in such a manner that we believe will eventually result in our arriving at a state in which we will feel comfortable and be at ease. Let us remember that these beliefs may be conscious or unconscious, and that the person reacting to a situation is certain, in his manner of perception and judgment at that moment, that he is taking the correct action. An observer, as often happens, may feel that the action had no sense. Basically this is due to the different personality structure of each individual.

In order to obtain a better understanding of why each individual reacts in his own characteristic manner the personality structure is divided into three parts each of which is constantly reacting with the others.

The first we call the id. It is what we are born with. Here we have the desires, cravings and drives that are present within oneself. It is the core of the personality. If we are hungry we want food, if something or someone is doing us mental or physical harm we want to either destroy it, remove it or run away from it. If we desire sex we seek a mate. These desires are innate, they are with us all the time and, although often we are not aware of them, we are constantly striving to fulfill them. These demands of the id keep a person constantly striving for those things which give him pleasure. As infants and small children our parents take care of us and supply the food, warmth and protection we want. As we grow older we gradually learn that what we want

Lecture presented on September 18, 1964, at Management Seminar sponsored by the Federal Business Association of Puerto Rico, at the Caribe Hilton Hotel, San Juan, Puerto Rico.

is not always obtained immediately.

We discover that there are others about us upon whom we are dependent.

The second part of the personality starts forming, the Ego or Self. It comprises those elements of the personality responsible for perceiving, reasoning, feeling, choosing, and doing. It is gradually formed from birth as we become aware of the environment and the people about us. It is the result of all our training, schooling, learning, and social activities. The ego listens to the demands of the id. It then studies the situation to determine how it can satisfy these demands. The action taken depends on the demands, the situation, and what the ego has learned in the past. The ego tries to act in such a manner that the demands of the id are satisfied and at the same time no harm comes to the personality.

While this is going on another factor comes into play. As we grow up and learn from our parents, teachers, and others in the environment, we form definite ideas and attitudes of what we believe is right and what is wrong. Some of these beliefs and attitudes become so ingrained in us that reactions to certain situations become automatic. We can, therefore, say that sometimes these responses are on an unconscious level. We have to respond to certain situations in a specific manner. Otherwise, even if we are not aware of the reason why, we feel uneasy, uncomfortable and even guilty. This part of the personality is called the Superego. It is the policeman governing both our conscious and unconscious demands.

As the personality develops, many frustrations arise. The final characteristic responses of an individual depends on how he has been able to cope with them. Too many successes easily obtained may lead to an overconfident person who is sure he knows everything. Too many failures may lead to the quiet submissive individual who is afraid to move out of the groove life has made for him.

The reason I gave this short and quite inadequate outline on the personality structure was to show how difficult it is to determine what may be the responses of individuals to specific situations. As managers and officers of large organizations you are interested in presenting to your staffs and employees situations that will induce responses resulting in improved or increased productivity of your organization. As you know, the methods used to produce results vary with the level to which your employees belong.

As we start to study Motivation, many difficulties arise. First is its definition. What is it? Let us say that it is a dynamic process producing a goal-oriented behavior. In our particular case let us also add that this behavior will lead to the improvement in the functioning of our organizations.

Another difficulty is its complexity. In order to motivate an individual you would have to know his personality make up. This, at the present time, is impossible, unless we put him thru a psychiatrical examination and psychological testing. This, on a superficial level is now being done in some organizations. At the present time, probably what would be best to determine the possible behavior of an individual is to study his behavior in the external environment, his internal physiological needs and his past experience. This in itself is difficult and complex.

Up to about 25 years ago the worker was more or less regarded as a machine. Under a certain set of conditions certain results were obtained. Only lately is the "human" aspect of the worker being studied and he is seen as a whole person whose feelings, attitudes and motivations at home, in society and within the organization react with his capabilities to produce his behavior. At the present time, we are more or less in a position in the

social sciences like that of the physical sciences with respect to atomic energy in the thirties. We know that past conceptions of man are inadequate and in many ways incorrect. We are beginning to see evidence that under proper conditions unimagined resources of creative human energy could become available under the organizational setting. It will take years of experimentation and exploration before this knowledge can be used by management in a practical manner.

At the present time it can more or less be truly stated that management's concept of the organization and the uses of human energy is as follows:

1. Management is responsible for organizing the elements of productive enterprises — money, material, equipment and people — in the interest of economic ends.

2. As to the people, management has to direct, motivate, and utilize their actions, modifying their behavior to fit the needs of the organization.

3. Without this active intervention some people would be passive or even resistant to organizational needs. They must, therefore, be persuaded, rewarded, and corrected — their activities must be directed, In other words management consists of getting things done by directing other people.

In addition, there are many widespread beliefs such as follows:

1. Man is lazy. He works as little as possible.

2. He lacks ambition, dislikes responsibility and prefers to be led.

3. He is inherently self centered, indifferent to organizational needs.

4. He is by nature resistant to change.

5. He is gullible, not very bright, easily deceived by the charlatan and the demagogue.

To perform its task, management has conceived of a range of possibilities between the following two extremes.

1. The hard approach using coercion and threat, close supervision and tight controls over behavior. This usually breeds counterforces: restriction of output, antagonism, militant unionism, subtle but effective sabotage of management objectives. It is especially difficult during times of full employment.

2. The soft approach by being permissive, satisfying peoples' demands and achieving harmony. The idea being that the people will be tractable and accept direction. This leads to harmony and also to indifferent performance. Some people take advantage of the soft approach. They continuously expect more, but give less and less. In general, the popular policy is between these two extremes.

From social science studies in the laboratory, the clinic, the schoolroom, the home and even to a limited extent in industry, suggestive findings show that these beliefs may be incorrect. The social scientist does not deny that human behavior in an organization is approximately what management believes. However, its findings suggest that it is not man's inherent nature, and that it is the consequence of organizations and management policy, philosophy, and practice. Now if this is so, what is the answer. At the present time social science cannot give the answer but from studies done it can indicate that conventional assumptions about the human side enterprise are inadequate.

We know that man is a wanting animal. As soon as one need is satisfied another takes its place. The process is unending. It continues from birth to death.

Man's needs are organized on different levels. The first is the physiological, or as stated at the start of this talk, the demands of the id. If he is hungry, needs shelter and protection, etc., that is enough to motivate him. As soon as these needs are taken care of, they will no longer motivate him. A satisfied need is not a motivator of be-

havior.

When the physiological needs are reasonably satisfied, needs at the next higher level begin to dominate man's behavior — to motivate him. He wants security. He is getting everything that is satisfying his physiological needs and he wants to be sure he will keep getting them. Any management policy or action that arouses uncertainty with respects to continued employment, reflects favoritism or discrimination, will motivate the worker towards changing his behavior. In our society and culture these two needs are fairly well taken care of among the majority of the people. In general, we can say that they cannot be used to motivate an individual's behavior.

After these needs are satisfied, the needs that are of the greatest significance to management and to man himself come into play. These are the social and egoistic. Man wants to be recognized by his society. He wants self-esteem, he wants to get ahead and he wants to be appreciated for his knowledge and competency. Unlike the lower needs, these needs are rarely satisfied. As soon as man satisfies some of them he wants more and more. In the typical organization few opportunities are given to workers at the lower level to satisfy these needs.

I believe we can safely state that the more man can satisfy these higher needs the happier and more contented he will be with his place in society. If he can get some of them in his organization, the organization and he will both be gainers. If he cannot obtain any from his organization he has to look outside for them. With today's social values, the more money he has the more he can obtain these higher needs or substitutes for them. The only place he can get money is from the organization he is working for, therefore, he will ask for higher salaries. Will the higher salary motivate his behavior and lead to greater productivity in his organization? In general, the answer is no. If the high salary is obtained thru a union, the union will get the credit. There is no need for him to increase his productivity. He sees about him others doing less than he and also getting the same salary. If he persuades his chief to raise his salary he will credit this to his own good argumentation. In fact, most of the salary increases which may be due to the organizations better tooling or better design, length of service increases, and profit sharing, do not lead to any change of the individual behavior towards increased productivity. In these increases no distinction is made by the management of the individual's behavior. However, they do reduce labor turnover.

In order to motivate the individual to change his behavior towards greater productivity, several essentials are required. The incentive given must depend directly on the individual's performance. The intent must be to earn more by producing more. The rewards must be certain and they must come promptly.

Bonuses and commissions are one method, provided the extra payments are for extra results and have nothing to do with the profits of the company. Individual and group incentive plans are another. Extra pay will be proportional to the extra productivity obtained. Where groups are concerned it has been found that the smaller the group, the better the results. In large groups there will always be someone who will produce less but will share in the extra earnings of the group. This usually leads to dissatisfaction and lower productivity of the group.

Merit plans which depend on the evaluation of the individuals performance at yearly or greater intervals, have shown very poor results as far as modifying the employees behavior towards greater productivity. The evaluation depends on the immediate supervisor. Studies

have shown that the supervisor, in general, remembers only what has occurred during the last 2 or 3 weeks before the date of the evaluation. The workers, knowing that they will soon be up for evaluation will improve their behavior. If the supervisor does remember unfavorable behavior in the past and rates the employees on this, dissatisfaction will arise among the employees, for the employees will remember what a wonderful job they have been doing during the last few weeks and feel that they should be judged on it. If the behavior of the employee is rated satisfactory, he can slip back to his old mode of behavior as soon as the rating is made official. This is noted by other employees and breeds dissatisfaction among them.

Let us repeat again what is required to motivate the behavior of the employee so that he will change his behavior and do more for the good of the organization. The incentive given must depend directly on the individual's performance. The intent must be to earn more by producing more. The rewards must be certain and they must come promptly. In addition, may I add, that it is also understood that the rewards will keep coming only as long as he is producing more.

Today, the importance of Motivation is being stressed more and more. At times too much emphasis is being placed on it. Let us remember that industry and organizational settings have made tremendous gains in the past thru such factors as ability, learning, equipment designs and conditions of work. Studies have shown, that to a small extent, motivation may compensate for lack of some of these factors. These studies have also demonstrated that motivation gave its best results when it was considered as one of the many factors that can lead to greater productivity of the worker. As a short example, motivation by itself cannot lead to any great change if ability is not present.

In order to bring about constructive changes, management must change its concepts of the organization and the uses of human energy. Its responsibilities remain the same, its leadership is essential in the interest of economic ends. It has to realize that man is not passive by nature and that he is resistant to organizational needs because the organization has made him so. The necessary task that management must undertake is to discover what arrangements can be made of the organizational settings and methods of operation that will motivate the employees toward that type of behavior that is directed toward the goals of the organization. It has to make conditions of work such, that the employee will have pride and increased self esteem in his work, that he will clearly see the objectives of the organization and that by using his capabilities and accepting responsibilities he himself, will direct his energy towards accomplishing the goals of the organization. Studies have shown that these possibilities are present in man and it is up to the organization to set up the necessary conditions that will make full use of this power. It is worth noting that the difference between the old and new concept of utilizing human energy is that of treating people as mature adults instead of as children. After many years of the latter, it will take a long time before the change can be made.

In order to develop plans for motivating workers, factors in and outside the working conditions must be taken into consideration. If working conditions are good and management is fair one pattern of motivation will appear. If pay is good and supervision is poor, another pattern will appear. If the worker is happy in his home life, one set of behavior will occur; if unhappy, another. In one study it was found that average production went up 2 percent when the worker was happy and dropped 7 percent when the worker was unhappy in his home life.

It appears obvious that an employee who is unhappy in his home life and feels dissatisfied with his job will not be motivated towards the right direction. Some of the causes of unhappiness and dissatisfaction that are job connected can be dealt with by the management if the management has knowledge of them. There are other causes that are beyond the capabilities or the area of responsibilities of the management. What we are interested in are those causes that can be helped by the management provided the management can discover what they are.

There are two approaches that can be utilized in attempting to reduce workers' dissatisfaction. One involves discovering the source of dissatisfaction and attempting thru administrative action to remove or change the conditions that rise to the dissatisfaction. The other approach has quite a different orientation. It involves dealing with the dissatisfaction at a personal level, seeking thru a counseling process to resolve the motivational and adjustment problems of the individual worker. Both of these procedures are now obviously being used by the immediate supervisor. That is, the supervisor having good knowledge of what his organizational goals are, is satisfied with his position because he can easily contact his superiors, gets enough self esteem and satisfaction from his work and has a stable personality. He can do it. If he is also a person in whom the workers have confidence, feel free to report their problems to him, then he can do a better job of it. If in addition the worker believes that this supervisor is genuinely interested in him, as a friend and advisor, and is able to bring his personal problems to him, then you have the ideal supervisor. This type of supervisor can do more to motivate the workers to use their own initiative towards organizational goals than anyone else. The trouble is that there are not enough supervisors showing these abilities. This lack may partially be due to the higher ups in the organization not giving the supervisor the opportunity to develop these assets.

Some organizations have initiated special departments whose function is to collect information by personal interview with the worker or by questionnaires. This type of information getting must be conducted on a highly confidential basis. If the worker is sure there will be no reprisals the information will be more reliable. The information obtained is tabulated and presented to top management where the data is used as a basis for setting policies and procedures designed to improve working conditions. By this method much valuable information is obtained regarding the worker's points of view and attitudes. At other times the information is too vague to be of any use and often the management already has knowledge of the information submitted. One important aspect of this method is the matter of by-passing supervisors. This tends to allay the fears of the worker that their complaints will be held against them by their immediate supervisor. This method also assumes that the supervisor is incapable of obtaining the information and passing it on to his superior and also that he is incapable of settling the problems by personal contact and counseling. The results of this method may be dissatisfaction among the supervisors who will feel hurt because management has no confidence in him and the worker can now go over him. However, the top management needs information to keep in mind the problems of personnel at all levels in the organization. Before this method is put into effect the objectives behind it should be clearly explained to all levels.

Another program being used in some organizations is Personal-Counseling. This takes into consideration that the lower needs of man such as the physiological and security are taken care of by the conditions of work.

It tries to determine how to motivate the worker by trying to discover the underlying causes of the worker's dissatisfaction whether they originate at the place of work, in the home or in society. At present it is being used more for the screening of new employees and promotion of old employees. The worker is put thru a series of psychological tests to determine if he has the ability and personality to do his job. At times this program is extended to keep continuous contact with all employees to ascertain whether they are satisfied with their jobs and are motivated. Persons directing this type of program are specialists in the social sciences. They cover all levels in the organization. The most important factor for the success of this type of program is that employees on all levels have confidencc in it and firmly believe that all information given to the counselor is and will be held confidential. The counselor tries to discover any form of dissatisfaction that may reduce the worker's ability and capacity. The counselor tries to have the employee express his dissatisfaction or problems no matter where they arise from. The employee is encouraged to talk about them and what he believes are the causes and how he, the employee can solve them. This is a form of psychotherapy. This verbalization allows the individual to get rid of pent up feelings, makes him more clearly sec the problems he has and often allows him to make the proper decision to solve the problems. These problems may be in or outside the job situation. During these interviews the counselor remains passive and does not try to solve the employee's problem even if he knows the answer. On account of this the employee cannot later state that the management is interfering with his home life. By confidential reports the counselor reports to the top management what types of dissatisfaction in the job situation he has discovered. When home problems are found he may keep employee coming to him until problem is solved or he suggests to employee where he can go for help. There are many variations in this type of plan. What type will be most effective, if any, time will tell.

Since the first two men joined forces towards a single goal, means of motivation have been used. As conditions changed, man formed tribes, clans, organizations, nations, etc. It was only because man saw advantages in them, that they were successful. In other words, man was motivated. At present, we are looking ahead to find more efficient means of motivation. Since the basic needs of man, at least in our culture, are fairly well taken carc of, we have to utilize the higher needs such as the social and egoistic to further motivate the employee towards furthering the goals of the organization. In searching for new methods top management should remember that the organization has arrived at its present size and efficiency because the methods of motivations used in the past were adequate.

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CASE REPORT

MYXEDEMA PRECEDING THYROTOXICOSIS IN GRAVES' DISEASE

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The development of thyrotoxicosis in a patient previously exhibiting myxedema is apparently rare. Sattler, in his book on Basedow's disease, relates a few instances of spontaneous evolution from myxedema to hyperthyroidism culled from an extensive review of the literature prior to 1907 (1). This sequence has been more recently reported in several patients with thyroid dysfunction associated with pituitary disease (2 - 6), in two cases of myxedema attributed to iodine ingestion (7, 8) and in a case with Hashimoto's struma (9).

We will describe an additional case in which this sequence was observed and consider its possible pathogenesis.

Case Report

A 23 year old mulatto male was initially diagnosed chronic bronchitis in 1944 at another hospital. In 1950 he entered this hospital because of progressive dyspnea. Bronchial asthma was diagnosed and he was treated with aminophylline. In 1953 a diagnosis of hematogenous tuberculosis was made at another hospital on the basis of roentgenologic findings. Sputum cultures were negative for tubercle bacilli. He was treated with isoniazide, streptomycin and para-amino-salicylic acid during the following two years, Examination in subsequent years failed to show evidence of active tuberculous disease.

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He was again hospitalized in 1959 with the history of painless swelling of the submandibular region (apparently submaxillary glands) and face. This subsided spontaneously in about two weeks. Two months later he developed low back ache for which medication thought to be a corticosteroid was prescribed by a physician. While taking this he noticed increasing fatigability, intolerance to cold and rapid weight gain. No unusual dietary history was elicited. He had taken no further antituberculous medication. Examination on admission showed the classical signs of myxedema. He weighed 190 lbs. The thyroid gland was not palpable. Sibilant rales were heard throughout both lung fields. Laboratory examinations showed a slight normochromic anemia, hypercholesterolemia, low BMR, T_3-RBC and thyroid radioiodine uptake (Table I). The serum was very turbid. Thyroglobulin autoprecipitin* was positive in the undiluted serum only.

Chest roentgenogram was negative. Electrocardiogram showed non-specific ST and T wave changes.

Under treatment with thyroid extract in dosages up to 125 mg daily, he improved slowly. He also received saturated solution of potassium iodide because of respiratory symptoms. He continued as an outpatient for about one year, the dose of thyroid being increased to 250 mg daily. He was then lost to follow-up during the following four years. The patient states, however, that he continued to take the prescribed medications (thyroid extract and potassium iodide) regularly.

On September 12, 1966 the patient was readmitted because of the insidious onset over a 3 month period, of exophthalmos, diarrhea, polyuria, tremulousness, weight loss and enlargement of the thyroid gland. He now weighed 146 lbs. The thyroid was diffusely enlarged but the right lobe was

**Hyland TA-Test ®, Hyland Laboratories, Los Angeles, Calif.*

TABLE I: SUMMARY OF THYROID FUNCTION TESTS

	Oct. 1959	Apr. 1961	Sept. 1966	Apr. 1967	May 1967
BMR	−29 percent	+22	+65	–	–
Cholesterol (mg/100 ml)	715	282	218	740	315
Thyroid ^{131}I uptake (percent):					
6 hours	2	–	64	3	–
24 hours	1	–	65	2	–
T3–RBC (percent)	–	12	18	8	8.9
PBI (μg/100 ml)	–	–	12	> 30	1.7

more prominent. It was not tender. There was moderate bilaterally symmetrical exophthalmos and he showed typical signs of thyrotoxicosis including tachycardia, bounding peripheral pulses, tremor of the extremities and wide arterial pulse pressure (140/60 mm Hg).

Laboratory data confirmed the diagnosis (Table I). Other examinations including serum proteins, calcium, phosphorous, transaminases, were normal. Thyroid antibody test was negative. Thyroid scanning showed irregularly distributed concentration of ^{131}I throughout an enlarged gland. Hypoactivity was noted in some areas, particularly in the right upper lobe.

Treatment with methimazole, 40 mg daily, and later Lugol's solution, was started in the hospital and continued as an outpatient. On February 28, when the patient was clinically euthyroid, a subtotal thyroidectomy was performed.

A large nodular thyroid gland was submitted to the laboratory. The nodules were ill defined and measured one to 5 millimeters. Microsections from its various lobes exhibited nodular hyperplasia with hypersecretion and involution pari passu. The hyperactive acini were lined with columnar epithelium, frequently with epithelial papillation, dilated and with active production of colloid (Fig. 1). The acini in the involuted areas were lined with cuboidal epithelium and showed a small amount of colloid. The stroma presented a lymphocytic follicular hyperplasia and some with germinal centers (Fig. 2). The nodules were usually partly enveloped by stromatous connective tissue.

Beginning two weeks after surgery the patient rapidly developed symptoms and signs of myxedema. He gained 10 lbs. in 13 days. Laboratory examinations confirmed the clinical impression (Table I). The exophthalmos remained unchanged. Because of the fact that the patient had received methimazole and Lugol's solution up to the time of surgery which could possibly have temporarily depressed the remaining thyroid tissue, no medication was prescribed until April 12. In view of the persistent myxedema, therapy with tri-iodothyronine was then started. Gradual improvement of symptomatology followed.

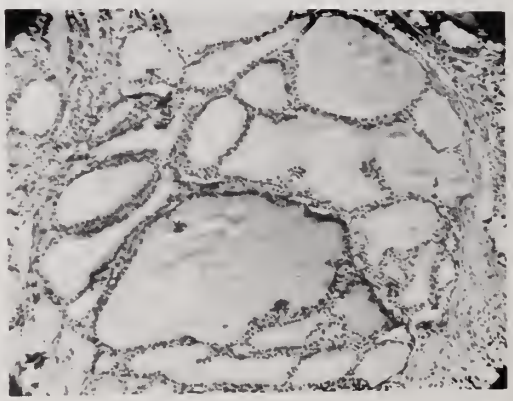


Fig. 1. Nodular area of epithelial hyperplasia and papillation of acini. The latter are filled and distended with colloid. Nodule is partly enveloped by fibrous stroma (H & E stain, X 200).

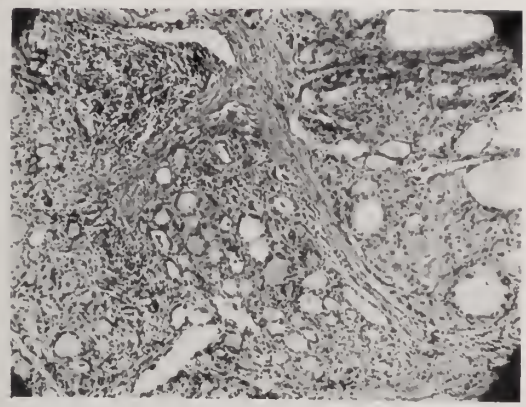


Fig. 2. Area of involution, fibrosis and follicular infiltrate with lymphocytes. Note small acini containing colloid (H & E stain, X 175).

Comments

This patient, who had been treated for chronic pulmonary disease with various medications, developed myxedema in 1959 following an acute illness which may have represented salivary gland or upper respiratory tract infection. Seven years later, while receiving treatment for hypothyroidism with dessicated thyroid, he developed thyrotoxicosis. Several possible explanations may be considered for the unusual sequence of alterations in thyroid function presenting in this patient.

Even though some of these are potential goitrogens, it does not seem likely that the antituberculous drugs received by the patient more than four years before or the brief course of a corticosteroid which he may have received prior to the onset of myxedema could have been its cause.

If the patient had, as the history suggests, transient enlargement of the salivary glands prior to the development of myxedema in 1959, the presence of iodism is a possibility. We have no record that iodides had been prescribed for his chronic pulmonary disease prior to this time, but the patient thinks he may have taken this medication. Thus iodine-induced goitre may have caused hypothyroidism. It is conceivable that discrete enlargement of the thyroid may have been overlooked in this obese patient. A relation between iodine-induced goitre and thyrotoxicosis has been suggested (10) and, in fact, thyrotoxicosis following iodine-induced goitre has been described (7, 8). The histological findings in the thyroid gland do not appear to support this possibility. The low radioiodine uptake by the thyroid is against this explanation (11). As this possibility was not thought of at the time, appropriate tests to rule it out were not performed.

Another possible explanation for the events in this case could be based on the mechanism proposed by Kriss et al (12). The initial illness which was apparently characterized by inflammation of the salivary glands may have been mumps. Mumps virus is apparently able to provoke a form of thyroiditis (13). This primary injury, resulting in transitory hypofunction, may have also stimulated the production of long-acting thyroid stimulator (LATS) leading eventually to hyperplasia of the remaining glandular elements and the development of thyrotoxicosis at a later time. Unfortunately, serial determinations of LATS were not carried out. The slight to moderate increase in fibrous tissue in the excised thyroid tissue could have been due to thyroiditis. The histological examination did not otherwise support this possibility.

The various manifestations of Graves' disease may at times present unusual patterns. Although the characteristic exophthalmos usually coincides with the development of thyrotoxicosis, it may precede it or it may follow remission of the metabolic disturbance brought about by irradiation or surgical ablation of the gland (14, 15). Exophthalmos is also sometimes seen in patients who were presently or formerly

hypothyroid and in euthyroid subjects in whom only very detailed study of thyroid function allows recognition of abnormalities (14, 15, 16). Localized myxedema, on the other hand, usually occurs in the presence of thyrotoxicosis (17).

In his extensive review, Sattler (1) includes myxedema among the possible presenting pictures of untreated Basedow's disease. Certain elements or the full clinical syndrome of hypothyroidism were observed in some cases to precede the onset of thyrotoxicosis. One could postulate that our case was an instance of this disease in which extraneous circumstances such as the administration of steroids, iodine, heterologous thyroxine or antituberculous drugs, or infection, altered the course of the disease. The histological findings in the thyroid gland are consistent with Graves' disease and would thus seem to favor this hypothesis.

Summary

The case is described of a 47 yr. old male who developed thyrotoxicosis while under treatment with thyroid extract for myxedema diagnosed 7 years before. Histological examination of the gland revealed changes consistent with Graves' disease. Several possible explanations for this sequence of events are considered. The authors favor the hypothesis that both myxedema and thyrotoxicosis in this man represented phases in the course of Graves' disease which may have been influenced by various circumstances including infection and medications received.

Acknowledgment

The histological material was reviewed by Frank B. Johnson, M. D., of the Armed Forces Institute of Pathology, Washington, D. C., who submitted the following diagnosis: Diffuse hyperplasia (toxic) with partial involution.

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CONVENCION ANUAL — NOV. 12-16, 1968

Hotel San Juan —— San Juan, Puerto Rico

PANCREATIC PSEUDOCYSTS WITH ABSCESS FORMATION

Roentgen Aspects

José A. Nassar, MD
Laszlo Ehrlich, MD, FACP, FACR
C. Guzmán Acosta, MD

Pseudocyst formation following acute or chronic pancreatitis occurs not infrequently; however, abscess complicating pseudocyst is unusual. Recently we had a case with precisely this type of complication; for this reason this particular case is presented.

Case Report

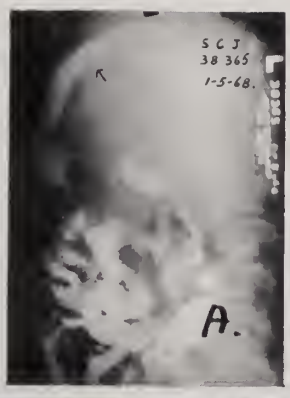
A 41-year old male patient was admitted on December 27, 1967 to our hospital with a history of epigastric pain of sudden onset 15 days prior to admission, rapidly becoming generalized, radiating to the back and accompanied by nausea and vomiting. The pain became constant and progressively worse. In 1965 he had been hospitalized in this institution and discharged with a diagnosis of acute pancreatitis. On admission the sclerae were slightly icteric, the blood pressure was 80/70 mm Hg, pulse 136 per minute, and oral temperature 99.2° F. The abdomen showed generalized rebound tenderness and no peristalsis. The admission impression was recurrent acute edematous pancreatitis.

Laboratory studies revealed a hemoglobin of 15.6 g/100 ml, hematocrit of 53 percent, WBC count of 22,781/cu. mm., with 76 percent neutrophils and 13 percent lymphocytes. Fasting blood sugar was 423 mg/100 ml, amylase 152 modified Somogy units /100 ml, lipase 0.9 units, total proteins 5.25 g/100 ml; albumin, 2.3 g, globulin 3.05 g/100 ml; indirect bilirubin, 2.2 mg/100 ml, direct bilirubin 0.75 mg/100 ml. The serum electrolytes: sodium 123, potassium 4.5, chlorides 87, carbon dioxide 18 mEq/L; and calcium 6.45 mg/100 ml. Upon admission the patient was placed on intravenous fluids and antibiotics. Radiographs of the chest and abdomen on admission were grossly negative.

Electrocardiogram on December 29th showed sinus tachycardia, clockwise rotation and non-specific T wave inversion. Radiographic examinations of the abdomen were again negative. Peristalsis returned, but the patient continued to do poorly. On December 31st an ill-defined mass in the epigastrium was felt for the first time and the diagnosis of pancreatic pseudocyst was made. On January 3rd a sudden decrease in hemoglobin to 6.7 g was noted. Blood transfusions were given and the next day examination of the patient showed dullness and fullness in the left flank accompanied by bluish discoloration of the skin. Chest radiographs revealed pleural effusion at the left base. Multiple films of the abdomen (Fig. 1) showed displacement of the stomach, duodeno-jejunal junction and transverse colon that were interpreted as a huge pseudocyst of the pancreas and splenomegaly. The mass continued to increase in size and a laparotomy was performed on January 8th. It revealed a large cystic mass at the lesser sac extending to the left flank and containing 1000 ml of brownish fluid. The contents were evacuated and a pancreatocystogastrostomy and gastrostomy were done.

The patient improved and on January 11th a barium swallow was done (Fig. 2). The study showed a patent cystogastrostomy and persistence of a large pseudocyst in the left upper quadrant. The patient continued to do clinically well and next day he was started on a liquid diet. Two days later he developed fever and left flank tenderness. Induration in this area was noted shortly after. Multiple films of the abdomen on January 16th (Fig.3) revealed evidence of tissue necrosis with gas in the area of the pancreas extending to the left of the abdomen inferiorly. Re-examination two days later including barium swallow (Fig. 4) again revealed a large retroperitoneal area of tissue necrosis; an abscess with fluid level in the left infradiaphragmatic area;

From the X-Ray Service, Veterans Administration Hospital, San Juan, P. R.



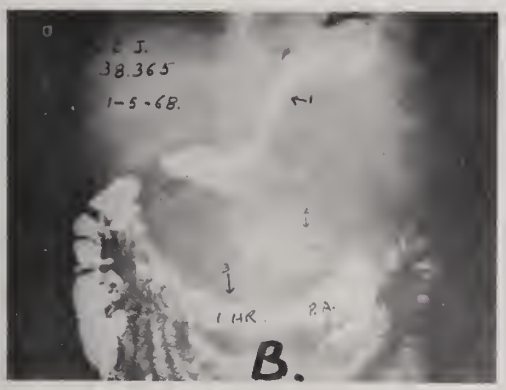


Fig. 1: A. Left lateral recumbent view of the stomach shows marked pressure on the posterior wall of the body (arrow) displacing the stomach anteriorly. B. One hour prone film also shows the extrinsic pressure involving the greater curvature of the body (arrow no. 1), and displacement of the duodeno-jejunal junction (arrow no. 2) and the transverse colon (arrow no. 3) inferiorly.

non-functioning cystogastrostomy; a fistula into the pancreatic area at the level of the gastric antrum; persistent pseudocyst.

In the meantime the patient continued with fever and abdominal tenderness. On January 11th a laparotomy was done. It showed a non-leaking gastrostomy; a patent cystogastrostomy; a large pseudocyst of the pancreas containing 500 to 700 ml of ash-colored fluid and blood clots, this was evacuated and drains inserted; a large retroperitoneal abscess in the left side containing 800 to 1000 ml of purulent fluid which was drained through a left flank incision. Culture from the pancreatic pseudocyst yielded a



Fig. 2: Fifteen minutes erect film following administration of a small amount of barium demonstrates patency (arrow) of the cystogastrostomy.



Fig. 3: Abdomen (supine) shows a conspicuous mottling (arrows) in the left upper abdomen extending to the right across the midline and inferiorly along the left flank to the level of the iliac bone. The left psoas is blurred.

pure growth of an intermediate coliform bacillus. Because of the patient's poor clinical condition no follow up films were obtained. Recurrent bleeding from the gastrostomy developed about three weeks after. On February 11th he again began to bleed from the gastrostomy and expired shortly after. Gross findings at post mortem examination revealed an acute retroperitoneal hemorrhage from erosive perforation of the splenic vein.

Discussion

In the evaluation of a patient with acute or chronic pancreatitis with pseudocyst, serial

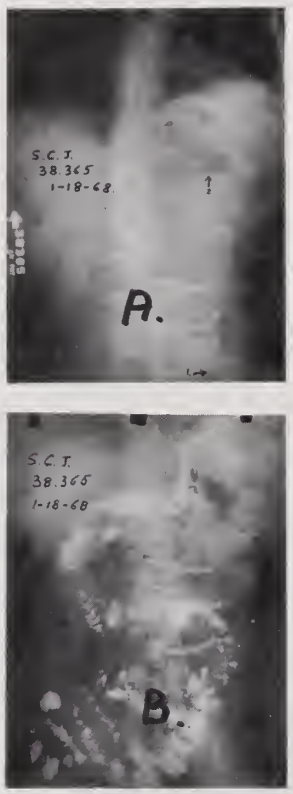


Fig. 4: A. Abdomen (erect) again shows the mottling in the left abdomen (arrow no. 1) a fluid level in the abscess cavity (arrow no. 2) and splenomegaly. B. Following barium ingestion, prone, shows non-functioning cystogastrostomy and a fistula (arrow) from the antrum into the pancreatic area.

roentgen studies of the abdomen are of paramount importance. Although not always revealing, the plain abdominal film may suggest a soft tissue mass. Further information may be obtained with a barium meal study. The lateral view is of particular value since it may show anterior displacement of the stomach. This is expected since most pseudocysts communicate with the secretory cells of the pancreas with outpouring of enzymes into any adjacent area, most commonly the lesser sac (1). The frontal views may show gastric displacement laterally or medially producing impressions along the greater or lesser curvature, fundus, body or antrum; also, any portion of the duodenum may be displaced in any direction (2). Films of the chest may show pleural effusion, as well as basilar atelectasis or pneumonitis or both (1). In a series of 39 cases of pancreatic pseudocysts demonstration of a mass lesion in a barium study was possible in 51 percent of the patients, calcification within the pancreas and evidence of pneumonitis or pleural effusion were noted in 20 percent and 10 percent respectively (3). On the plain film of the abdomen, the lesser sac abscesses following pancreatic necrosis may manifest themselves radiologically as innumerable small gas bubbles or as larger gas collections with fluid levels (4). The case presented demonstrates the above roentgen criteria for diagnosis of pseudocyst and abscess formation complicating the surgical procedure (cystogastrostomy). It is of interest that the abscess developed within five days after the operation. Although the current literature concerning this complication is uninformative, it is felt that abscess should be considered as an early potential complication, and the plain film should be taken routinely in search for it.

Pseudocyst may be subject to other complications of interest to the radiologist. Such are splenic vein compression producing splenomegaly and varices, common bile duct obstruction, hemorrhage into the gastrointestinal tract or into the cyst, rupture into the portal vein or intraperitoneally and gastrocolic fistula (5). In the case presented, recurrent bleeding through the gastrostomy further complicated the patient's condition, and he subsequently died from a massive hemorrhage due to erosion of the splenic vein.

Summary

A case of chronic pancreatitis with pseudo-

cyst formation and abscess complicating surgery was presented. The roentgen manifestations are discussed.

Resumen

Se presenta un caso de pancreatitis crónica con seudoquiste y formación de absceso complicando una cistogastrostomía. Se discuten los hallazgos radiológicos en estas lesiones.

Acknowledgment

Our gratitude is due to the members of the Surgical Service of this hospital for their cooperation in the presentation of this case.

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BILHARZIASIS EN PUERTO RICO AYER Y HOY

Apreciación Clínica

Rafael Rodríguez Molina, MD

Hemos creído oportuno y conveniente dar a conocer a la clase médica de nuestro país ciertas observaciones recogidas en la clínica externa de Bilharzia ubicada en el Centro Médico de Puerto Rico. La clínica es una actividad del departamento de Medicina de la Escuela de Medicina, y opera bajo la dirección del Dr. Francisco Ramos Morales, jefe del departamento. Fue establecida hace varios años, y a ella acuden pacientes de toda la isla referidos por las unidades y centros de salud pública y por médicos particulares. La entrevista y el examen de nuevos pacientes y las visitas subsiguientes se practican con miras al estudio de los distintos aspectos de la enfermedad, y lo que es más importante la observación cuidadosa y tratamiento del enfermo.

Como es de esperarse allí van niños y adultos de ambos sexos. El grupo más numeroso que hemos observado lo es el de varones de 10 a 15 años. Ello concuerda con los resultados obtenidos por el Dr. José F. Maldonado (1) del departamento de Zoología Médica de la Escuela de Medicina, en el sentido de que son los varones de 10 a 15 años los que muestran la más alta incidencia de infección con el parásito en Puerto Rico.

No es nuestra intención presentar estadísticas para respaldar lo que vamos a decir más adelante, por la sencilla razón de que no las tenemos. Sin embargo deseamos y nos atrevemos a comparar en términos generales y a manera de apreciación clínica, la enfermedad como se manifiesta ahora, con la que antaño se observaba en la Escuela de Medicina Tropical, década del 1930 al 40, y luego la que se estudió en el servicio militar durante el período 1942 al 1947.

A nuestro parecer el tipo de enfermedad que ahora se presenta es más benigno con manifestaciones clínicas menos marcadas. Por ejemplo: con frecuencia se nota sintomatología leve gastro-intestinal (pesadez, llenura, dolor abdominal), sin diarrea. Todo ello asociado a biopsias rectales conteniendo numerosos huevos, y más de 300 huevecillos por gramo de heces fecales (técnica de concentración, que parece indicar una infección moderada). Opinamos que en el ayer, el historial arriba mencionado estaría más frecuentemente acompañado de diarrea con o sin sangre.

Creemos, además, que el porcentaje de pacientes asintomáticos tanto en niños como adultos es más alto que el de alrededor de 50 porciento observado anteriormente. Son más raros los casos que presentan un cuadro avanzado y terminal con franca hipertensión portal, hiperesplenismo, acompañado de emaciación extrema. En el término de un año que venimos asistiendo a la clínica de Bilharzia, no hemos observado un solo caso con manifestaciones cardio-pulmonares.

Si bien es verdad que se ven niños varones con hígado y bazo agrandados, el estado general de salud y la nutrición no parecen estar muy afectados, ni se nota anemia marcada o leucopenia. Se diría que la evolución de la enfermedad como que está estancada, sin afectar

en mucho el estado de salud del paciente. Muchos de ellos no se quejan y asisten regularmente a la escuela.

¿A qué se debe, nos preguntamos, tales cambios por fortuna favorables, del ayer al hoy? La infección es evidente tanto hoy como ayer, a juzgar por los resultados de exámenes de excreta y biopsias rectales. Es lamentable que no dispongamos aún de una técnica para determinar el número de gusanos adultos que tiene cada enfermo. Pero sí es un hecho aceptado que el estado de nutrición y la alimentación han mejorado en nuestro país en los últimos 30 años—y por ende la defensa o resistencia del individuo hacia el parásito parece que ha aumentado. Además, estudios practicados en niños de edad escolar en aquellas áreas, como Guayama, en que se hiciera con anterioridad una campaña contra el caracol huésped intermediario empleándose agentes químicos, han indicado un índice más bajo de infección que el obtenido en áreas donde no se había efectuado tal campaña. De hecho se ha encontrado que la incidencia de infecciones en niños de seis años se ha mantenido en cero, en la isla de Vieques, luego de una campaña de control continuado por varios años (2).

Un aspecto que no ha variado mucho del ayer al hoy es el hecho de que con frecuencia el paciente con Bilharzia nos presenta otros parásitos, nemátodos intestinales tales como la uncinaria, el ascaris y el trichuris. En cuanto a la uncinaria, ahora se manifiesta menos intensa que antaño.

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EDITORIAL

NEGRO, CAUCASIAN OR PUERTO RICAN

A recent article in a leading medical journal dealing with a disease contracted by a group of American soldiers in Viet Nam, carefully describes clinical material said to include Caucasians, Negroes and Puerto Ricans. This type of accounting, which suggests confusion on the part of the authors (and perhaps the journal editors too) as to the anthropological meaning of the word Puerto Rican, is not unusual in medical literature.

This improper use of the designation Puerto Rican as if a particular race were implied, may be due to our multiracial origins and the extensive intermixture that has characterized Puerto Rican history. The intricacies of our political status may be an additional source of bewilderment for some.

The attainment of a smooth and peaceful process of a racial amalgamation is an accomplishment of which the people of Puerto Rico are certainly proud. It should be noted, on the other hand, that other national groups usually classified as Caucasian also are the product of extensive racial admixture (1).

It would seem that in situations where the racial background of a patient has medical significance, this segregation should be made as accurately as possible by the use of terms with well established meaning. Where an individual subject is obviously the product of racial mixture descriptive terms such as mulatto, mestizo, etc. should be used.

Elsewhere in this issue some aspects of this question are discussed in some detail by a well qualified authropologist.

Julio V. Rivera, MD

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Sex

In general, trends for osteoarthritis by body measurements are roughly similar for both sexes. On the whole, however, there appears to be a somewhat stronger association between body measurements and OA for women than for men.

Age

The age group 45-54 appears to show the strongest relationship between body measurements and osteoarthritis. In the older age groups (55-64 and 65-74) the relationship becomes much weaker for OA of the hands. The decrease in strength is some what less for OA of the feet.

Discussion

Although the sample population of the Health Examination Survey was different in composition from the other groups previously studied, the findings of the HES were in general in agreement with those of the other studies. It is thus quite likely that in humans, at least, there is an association between body measurements and osteoarthritis. This association is present in both weight-bearing and nonweight-bearing joints. The relationship appears to be much stronger for those body measurements which denote body and limb girths and breadths rather than lengths.

Body fat, as determined by skinfold measurements, appears to be positively correlated with osteoarthritis. However, a muscle factor is probably also involved. This may be demonstrated by the strong trend observed for osteoarthritis of the hands in men with increasing arm girths, while right arm skinfold thickness has little effect on osteoarthritis of the hands (in men). The diameter of the upper arm, corrected for subcutaneous fat, can be used as a criteria of muscularity in men.

Some attempts have been made to determine the effect of obesity experimentally in animals. Silberberg found that the incidence of osteoarthritis in underfed Strain A mice was lower and that lesions appeared later than in the *ad libitum* fed controls. On the other hand Mickelsen and others observed that bodyweight restriction produced by calorie reduction in Strain STR/IN mice which otherwise became obese spontaneously produced no reduction in either the severity or incidence of osteoarthritis. One possible explanation of these conflicting findings is the use of two different strains of mice in the studies.

Regardless of the presence or absence of a relationship between obesity or body measurements and osteoarthritis in mice the findings of the Health Examination Survey and other studies cited appear to establish the presence of such a relationship in man. The data available at present unfortunately are not sufficient to allow the formation of any firm conclusions in regard to the biological mechanism involved in this relationship; however,

a few hypotheses can be offered. Excess weight undoubtedly is an important factor in causing excess strain on weight-bearing joints. In addition, muscle bulk tends to increase with increased physical work or exercise. Excess usage of the joints involved may result in increased joint wear and tear and a greater incidence of microtrauma. Bauer and Bennett compared the roentgenographic appearance of symmetrical joints in humans who subjected one joint to constant use or unusual trauma. For example, roentgenograms of one patient revealed extensive arthritic changes with loose-body formation in the right knee whereas the left knee showed very minimal change. This patient had operated a treadle machine for 30 years. In doing so she was required to flex and extend her right knee hundreds of times a day thereby subjecting this joint to unusual use for 30 years.

Another possible hypothesis to be investigated is the effect of an excess quantity of some component of the diet, such as fat, directly on the joints. Finally body build and osteoarthritis may be connected on a genetical basis which may link specific body types with a hereditary predisposition to early development of osteoarthritis.

Reproduced from National Center for Health Statistics, Series 11, Number 29 - U. S. Department of Health, Education and Welfare.

NOTICIAS

Cámara de Delegados

REUNIONES ADMINISTRATIVAS

Sábado, 9 de noviembre - 10:00 a.m.

La Cámara de Delegados celebrará su primera reunión en el Salón de Conferencias de la Asociación Médica de Puerto Rico.

A esta reunión deberán asistir, además de los miembros de la Cámara, los Presidentes de Secciones de Especialidad, de Juntas y Comités de la Asociación Médica. Regirá la siguiente agenda:

1. Invocación.
2. Constitución de la Cámara.
3. Informe Comité de Credenciales.
4. Lectura y aprobación del acta de la reunión ordinaria celebrada el 6 de julio de 1968 en Mayagüez.
5. Informes: Presidente, Secretario, Tesorero, Comité de Finanzas y Delegado AMA.
6. Acto de Entrega a la AMPR por el Club Exchange de Round Hill del Freedom Shrine.
7. Receso para almuerzo.
8. Presentación de Resoluciones e Informe del Comité de Resoluciones.

Martes, 12 de noviembre - 2:30 p.m.

La segunda reunión de la Cámara se celebrará en el domicilio de la AMPR. Se observará el siguiente orden:

1. Llamada al orden e Informe Comité de Credenciales.
2. Informes Distritos Este, Sur, Occidental y Norte.
3. Resoluciones pendientes.
4. Informe del Comité de Nominaciones.
5. Elección de funcionarios para el año 1968-69.

Sábado, 16 de noviembre - 12:00 m.

Asamblea General

Toda la matrícula está citada para esta Asamblea General Extraordinaria, que tendrá lugar en el Salón Isla Verde del Hotel San Juan, para considerar enmiendas al Reglamento del Auxilio Médico Mutuo.

NOTA: Las reuniones administrativas se regirán por la Constitución y el Reglamento de la Asociación.

SEXAGESIMA SEXTA CONVENCION ANUAL DE LA ASOCIACION MEDICA DE PUERTO RICO

Sesión Inaugural

Martes, 12 de noviembre de 1968 8:00 p.m.
Salón Isla Verde
Presidirá: José Fernández Martínez, MD

1. Invocación.
2. Palabras de bienvenida y presentación de invitados
José Fernández Martínez, MD
3. Presentación de Premios y Entrega de Distintivos
José A. Alvarez de Choudens, MD
a) Premios del Certamen de Escuela Superior, "La Medicina en la Era del Espacio".
b) Premio al mejor estudiante de la Escuela de Medicina de la Universidad de Puerto Rico, Clase de 1968.
c) Premio "Dr. Manuel Quevedo Báez" al médico que ha obtenido el mejor promedio en los exámenes de reválida durante el año 1968.
d) Premio "A. H. Robins" al Médico del Año.
e) Distintivos a los médicos que este año han cumplido 30 años como miembros de la Asociación Médica de Puerto Rico.
4. Breves palabras.
Dwight L. Wilbur, MD
5. Discurso Presidencial
José A. Alvarez de Choudens, MD
6. Recepción Presidencial

Miércoles, 13 de noviembre - 9:00 a.m.
Salón Isla Verde
Presidirá: Francisco Olazábal, Jr., MD

9:00 a.m. The Role of the Physician in the Sexual

Re-education of the Adult, Víctor Bernal y del Río, MD

9:20 a.m. - Criminal Non-Accountability and Psychiatry, John L. Simon, MD

9:40 a. m. - Long Term Therapy of Tropical Sprue with Unabsorbable Sulfa Drugs, Ricardo Guerra, MD, Norman Maldonado, MD, Enrique Horta, MD and Enrique Pérez Santiago, MD.

10:00 a.m. - New Perspectives in Allergic Disease, John P. McGovern, MD

10:30 a.m. - Emulsion Therapy in Food Allergy, Angel M. Marchand, MD

10:50 a.m. - Rationale of Injection Therapy Based on Immunological Studies, John T. Connell, MD

11:20 a.m. - Epidemiology of Bundle Branch Block in Puerto Rico, Ramón M. Suárez, MD and Ramón M. Suárez, Jr., MD.

11:40 a.m. - Wilms' Tumor: The Experience at I. González Martínez Hospital, José M. Tomé, MD

12:00 m. - Almuerzo - Cortesía de la Cruz Azul de Puerto Rico.

Miércoles, 13 de noviembre - 2:00 p.m.

Salón Isla Verde
Presidirá: Mario R. García Palmieri, MD

2:00 p.m. - Current Management of Fungus Diseases of the Lung, Howard A. Buechner, MD

2:30 p.m. - The Sources of Bilirubin: Physiological and Clinical Studies, Stephen H. Robinson, MD

3:00 p.m. - New Pulmonary Syndromes, Howard A. Buechner, MD

3:30 p.m. - Bilirubin Formation in Bone Marrow and Liver: Implication for Disease States, Stephen H. Robinson, MD

4:00 p.m. - Pathogenesis and treatment of Renal Hypertension, José L. Cangiano, MD and Víctor Vertes, MD

4:30 p.m. - The Control of Cardiac Arrhythmias in Patients with Acute Myocardial Infarction, William J. Grace, MD

5:00 p.m. - Diagnosis and Treatment of Functional Gastrointestinal Disorders, Dwight Wilbur, MD

Miércoles, 13 de noviembre - 8:00 p.m.

Salón Isla Verde

8:00 p.m. - Conferencia Anual "Dr. Ramón M. Suárez". Introducción: Dr. José A. Alvarez de Choudens. Presentación: Dr. Elí A. Ramírez Conferenciante: William B. Castle, MD. Tema: "Lessons in the Study of Megaloblastic Anemias".

Jueves, 14 de noviembre - 9:00 a.m.

Salón Isla Verde
(Sesión auspiciada por el Hospital de la Capital)
Presidirá: Fernando A. Batlle, MD

9:00 a.m. - Pure Red Cell Anemia: Presentation of Two Cases, A. Sabater de Valdés, MD, Mercedes A. de Torregrosa, MD and A. Barquet Chediak, MD

9:20 a.m. - Polycythemia Vera: Report of 17 Cases, Rafael A. Rizek, MD, Miguel A. Ramos, MD, Lillian Conde, MD and Ernesto J. Marchand, MD

9:40 a.m. - Mandibular Reconstruction in Patients with Oral Carcinoma Using the Patient's Own Mandible after Autoclaving, Héctor M. Alvarado, MD

10:00 a.m. - Current Management of Tracheo-Esophageal Fistula, Cameron Haight, MD

10:30 a.m. - Results of Open Heart Surgery at the San Juan City Hospital, Efraín A. Defendini, MD, Jorge O. Just Viera, MD and J. L. Rodríguez Pagán, MD

10:50 a.m. - Medical Treatment of Dissecting Aneurysm of the Aorta, Francisco Olazábal, MD and Luis G. Borrego, MD

11:10 a..m. Hyperglycemic Hyperosmolar Coma, Agustín M. de Andino, MD, Juan Enrique Rizek, MD, René Silva, MD and Lillian Conde, MD

11:30 a.m. - Experiencia Personal en el Tratamiento Quirúrgico de las Lesiones Cardíacas Adquiridas, Enrique García Ortiz, MD

12:00 m. - Almuerzo - Cortesía de los Hospitales Auxilio Mutuo, Del Maestro, Doctor's, Instituto Oftálmico, Mimiya, Pavía, Presbiteriano, San Carlos y San Jorge.

Jueves, 14 de noviembre - 2:00 p.m.

Salón Isla Verde
Presidirá: Aníbal Lugo, MD

2:00 p.m. - Common Orthopedic Problems in the Lower Limbs of Children, Robert B. Salter, MD

2:30 p.m. - Choices Among Antibiotics for Children, Alex J. Steigman, MD

3:00 p.m. - Complexities of Herpes Simplex Virus, Alex J. Steigman, MD

4:00 p.m. - Experiencia Personal en el Tratamiento Quirúrgico de las Cardiopatías Congénitas, Enrique García Ortiz, MD

4:30 p.m. - Panel: Medical Ethics and Contract Practice of Medicine, Walter J. Benavent, MD, Moderator, Alfred W. Axtmayer, MD, Carlos E. Bertrán, MD and José A. Alvarez de Choudens, MD.

Viernes, 15 de noviembre - 9:00 a.m.
Salón Isla Verde
(Sección Auspiciada por el Hospital de Veteranos)
Presidirá: C. José Ferraiouli, MD

9:00 a.m. - Fat Embolism: Patho-Physiology and Treatment, José H. Amadeo, MD
9:20 a.m. - Meningo-Encephalitis due to Listeria Monocytogenes, Fernando A. Córdova, MD and María Medina, MS
9:40 a.m. - Velocity Conduction Studies in Tropical Sprue, Herman J. Flax, MD, Arturo S. Lluveras, MD, Andrés Rodríguez, MD and Manuel Picó, MD
10:00 a.m. - Extensive Small Bowel Resection, José D. Pagán Pagán, MD and Edward Hammond, MD
10:20 a.m. - Comparison of Van de Kamer and Friedner Methods for Total Fecal Fat Determinations, Marta Cancio, PhD
10:40 a.m. - Automation in Patient Care, William A. Cherry, MD
11:10 a.m. - Clinico Pathological Conference, William B. Castle, MD and G. Ramírez de Arellano, MD
12:00 m. - Almuerzo, Cortesía de Seguros de Servicio de Salud.

Viernes, 15 de noviembre - 2:00 p.m.
Salón Isla Verde
Presidirá: Lillian Haddock, MD

2:00 p.m. - Medical Complications in Patients Undergoing Peritoneal Dialysis, José L. Cangiano, MD, Thomas Kuruvila, MD, Biman Kastagir, MD and Víctor Vertes, MD
2:20 p.m. - Histopathological Changes of Jejunal Mucosa in Tropical Sprue - Review of 600 Biopsies, Francisco Febles Vizcarrondo, MD
2:40 p.m. - Unusual Neurological Syndromes in Hyperthyroidism, L. P. Sánchez Longo, MD, Lillian Haddock, MD, René Silva, MD and Rafael Berríos Martínez, MD
3:00 p.m. - Coagulation Studies in Patients on Oral Contraceptives, Elizabeth B. Connell, MD
*3:30 p.m. * - Panel: Aspectos Médico-Legales en la Medicina Industrial y Compensación,* Participantes: Profesor Samuel B. Horowitz, Roberto Angleró, MD, Lcdo. Eddie Gaud Caballero, Herman J. Flax, MD, Héctor R. Torres, MD and Lic. R. Buscaglia, Jr. - Mantenedor.
* - Se llevará a efecto en la Sección "C" del Salón Isla Verde.
4:00 p.m. - The Physicians Abandonment of Moral Leadership, Nicholas P. Dallis, MD
4:30 p.m. - The Treatment of Brain Tumors by Radiation Therapy, Robert Pérez Tamayo, MD
5:00 p.m. - Electrodiagnosis: What the Up-To-Date M.D. Should Know, Eduardo Busó, MD

Presidirá: Amaury Capella, MD
8:00 p.m. - Panel: Obesidad: Causas, Peligros y Control, Participantes: Nelson A. Fernández López, MD, Mantenedor, Manuel Paniagua, MD, Luis Polo, MD, Mario R. García Palmieri, MD and Agustín M. De Andino, MD

Sábado, 16 de noviembre - 9:00 a.m.
Salón Isla Verde
(Sección Auspiciada por la Escuela de Medicina de la UPR)
Presidirá: José E. Sifontes, MD

9:00 a.m. - Tropical Sprue in Children, Pedro J. Santiago Borrero, MD and Norman Maldonado, MD
9:20 a.m. - Saline Water Diuresis, J. Santos Martínez, MD
9:40 a.m. - Studies in Infant Diarrhea IV Composition of Jejunal Fluid after a Single Feeding, Helen Rodríguez de Curet, MD and Ramón Torres Pinedo, MD
10:00 a.m. - Cross Reactivity of Anti-NPH Insulin Antibodies in Experimental Animals, Mirta Rosas del Valle, MD and E. Toro Goyco, MD
10:20 a.m. - Clinical and Biochemical Analysis of 14 Cases with Primary Hyperparathyroidism, Lillian Haddock, MD, Julián Vázquez Plard, MD, Francisco Aguiló, Jr., MD, María del Carmen Vázquez, BS, MT and Francisco L. Raffucci, MD
10:40 a.m. - The Effect of Aldosterone on Membrane Potential of Cardiac Muscle Fibers, W. C. de Mello, MD
11:00 a.m. - Systemic Strongyloidiasis in Immunologic Deficiency Diseases, Ezequiel Rivera, MD, María Castillo, MD, Norman Maldonado, MD, Germán E. Malaret, MD, César Quiñones Díaz, MD and Enrique Vélez García, MD
11:20 a.m. - Reflux Esophagitis, Relation to Hiatal Hernia and its Management, Francisco L. Raffucci, MD, F. E. Oliveras, MD, E. Marquez, MD, Rosendo Ríos, MD and E. Vázquez, MD
11:40 a.m. - Studies in Tropical Sprue: Familial Incidence of Small Intestinal Abnormalities Among Relatives of Patients with Tropical Sprue, A. A. Cintrón Rivera, MD, J. Acosta Matienzo, MD, F. Febles Vizcarrondo, MD and G. Valls Ferraiouli, BS, CMT
12:00 m. - Asamblea General Extraordinaria de la

AMPR - Asunto Enmiendas al Reglamento Auxilio Médico Mutuo.

1:00 p.m. - Almuerzo - Cortesía de la Sociedad Médica Distrito Este

1:30 p.m. -Toma de Posesión de la nueva Directiva.

PROGRAMA AUDIOVISUAL
Preparado por el doctor Antonio R. Silva, Jr.

Películas científicas que serán exhibidas en el Salón El Chico, Hotel San Juan:

Miércoles 13

2:00 p.m. - "Current Concepts of Estrogen Replacement Therapy" - AYERST (32 min.)
2:35 p.m. - "Total Cesarean Hysterectomy" - SANDOZ (25 min.)
3:05 p.m. - "The Medical Witness" - GEIGY (34 min.)
4:45 p.m. - "Drug Induced Depression - Fact or Fallacy" - CIBA (16 min.)

Jueves 14

2:00 p.m. - "Diagnosis of Congenital Heart Disease" - GEIGY (22 min.)
2:30 p.m. - "Locomotion of Cancer Cells in Vivo" - UPJOHN (28 min.)
3:05 p.m. - "Visceral Organ Transplants" - UPJOHN (30 min.)
3:40 p.m. - "Viruses and Cancer" - GEIGY (13 min.)
4:00 p.m. - "Modern Concepts of Epilepsy" - AYERST (24 min.)
4:30 p.m. - "Mitral Valve - Dynamic Pathology and Surgery" - SQUIBB (19 min.)

Viernes 15

2:00 p.m. - "Mechanical Concerto of Madness" - SANDOZ (21 min.)
2:25 p.m. - "The Doctor Defendant" - MERRELL (30 min.)
3:00 p.m. - "Hypnosis as Sole Anesthesia for Cesarean Section" - UPJOHN (27 min.)
3:30 p.m. - "Circulatory Response to Vasopressor Drugs" - CIBA (25 min.)
4:00 p.m. - "The World of the Schizophrenic" - SANDOZ (21 min.)
4:25 p.m. - "Juvenile Polyps of the Colon" - SQUIBB (10 min.)

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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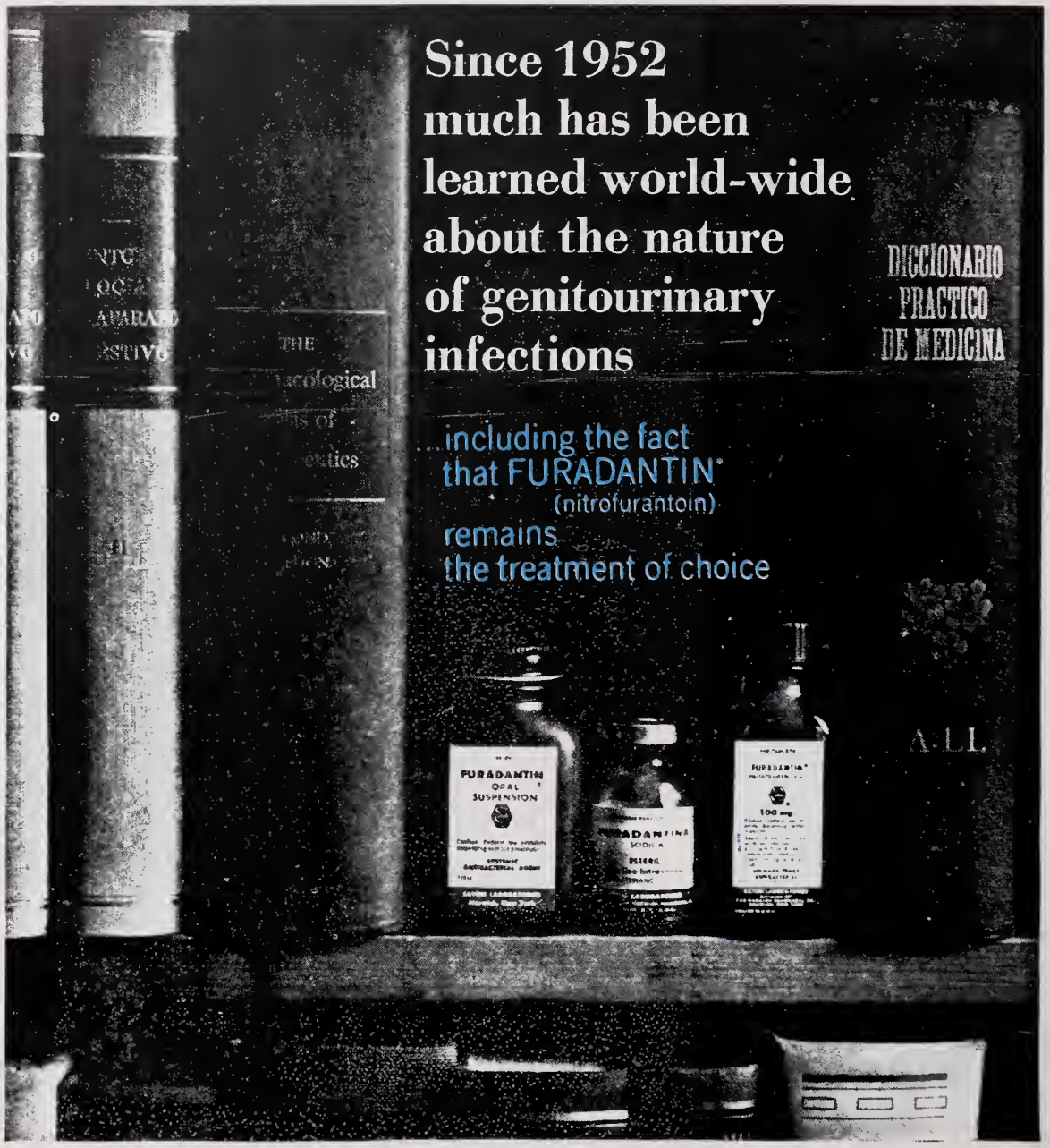
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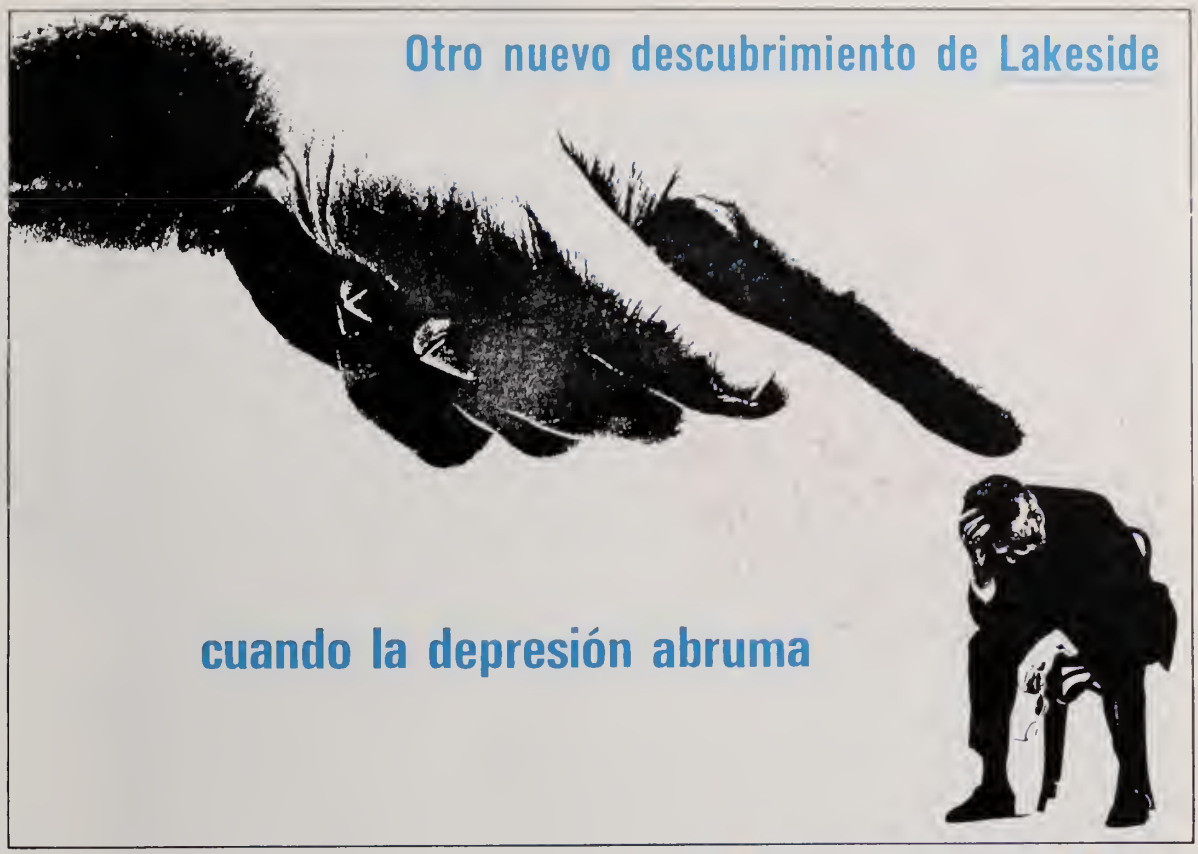
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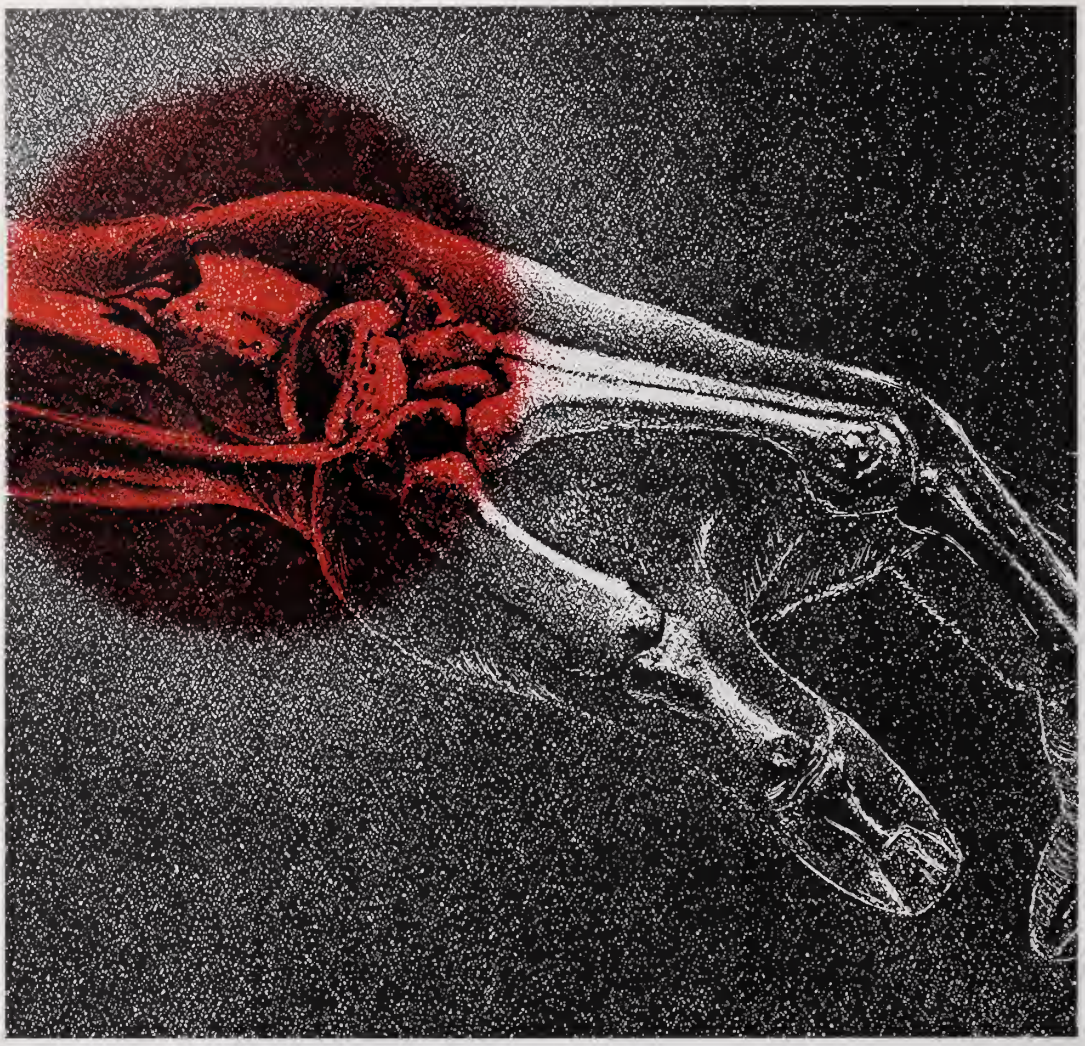
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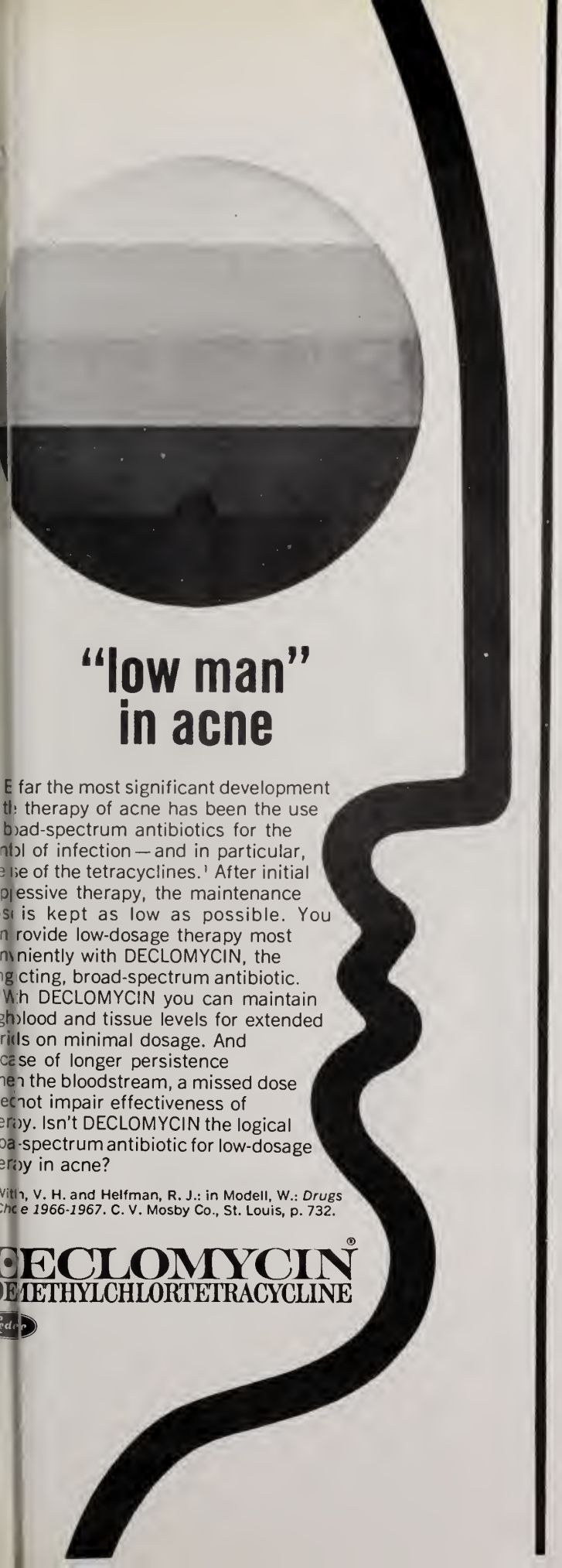
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1. Cirelli, M. G.: Delaware M. J. 34:159 (June) 1962.

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DECLOMYCIN Demethylchlortetracycline should b equally or more effective therapeutically than other tetra cyclines when the offending organisms are tetracycline sensitive.

Contraindication: History of hypersensitivity to demethy chlortetracycline.

Warning—In renal impairment, usual doses may lead t excessive accumulation and liver toxicity. Under sucl conditions, lower than usual doses are indicated, and, i therapy is prolonged, serum level determinations may b advisable. A photodynamic reaction to natural or artifi cial sunlight has been observed. Small amounts of drug and short exposure may produce an exaggerated sun burn reaction which may range from erythema to severe skin manifestations. In a smaller proportion, photo allergic reactions have been reported. Patients should avoid direct exposure to sunlight and discontinue drug a the first evidence of skin discomfort. Necessary subse quent courses of treatment with tetracyclines should be carefully observed.

Precautions—Overgrowth of nonsusceptible organisms may occur. Constant observation is essential. If new infections appear, appropriate measures should be taken. In infants, increased intracranial pressure with bulging fontanels has been observed. All signs and symptoms have disappeared rapidly upon cessation of treatment.

Side Effects—Gastrointestinal system—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes. A rare case of exfoliative dermatitis has been reported. Photosensitivity; onycholysis and discoloration of the nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. Teeth — dental staining (yellow-brown) in children of mothers given this drug during the latter half of pregnancy, and in children given the drug during the neonatal period, infancy and early childhood. Enamel hypoplasia has been seen in a few children. If adverse reaction or idiosyncrasy occurs discontinue medication and institute appropriate therapy.

Average Adult Daily Dosage: 150 mg q.i.d. or 300 mg b.i.d. Should be given 1 hour before or 2 hours after meals, since absorption is impaired by the concomitant administration of high calcium content drugs, foods and some dairy products. Treatment of streptococcal infections should continue for 10 days, even though symptoms have subsided.

Capsules: 150 mg; **Tablets:** film coated, 300 mg, 150 mg, and 75 mg of demethylchlortetracycline HCl.

DECLOMYCIN®
DEMETHYLCHLORTETRACYCLINE

LEDERLE LABORATORIES, A Division of
American Cyanamid Company, Pearl River, New York

Lederle



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but we should do something about that extra weight you're putting on."

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ntraindications: Dextro-amphetamine sulfate: In perexcitability and in agitated prepsychotic tes. Previous allergic or idiosyncratic reactions meprobamate.

ecautions: Use with caution in patients hyper-nsitive to sympathomimetic compounds, who ve coronary or cardiovascular disease, or are erely hypertensive.

Dextro-amphetamine sulfate: Excessive use by stable individuals may result in psychological pendence.

Meprobamate: Careful supervision of dose and ounts prescribed is advised, especially for pa-nts with known propensity for taking excessive antities of drugs. Excessive and prolonged use susceptible persons, e.g. alcoholics, former ad-ts, and other severe psychoneurotics, has been orted to result in dependence on the drug. ere excessive dosage has continued for weeks months, reduce dosage gradually. Sudden with-wal may precipitate recurrence of preexisting nptoms such as anxiety, anorexia, or insomnia; withdrawal reactions such as vomiting, ataxia, mors, muscle twitching and, rarely, epileptiform zures. Should meprobamate cause drowsiness visual disturbances, reduce dosage and avoid eration of motor vehicles, machinery or other tivity requiring alertness. Effects of excessive al-nol consumption may be increased by meproba-te. Appropriate caution is recommended with tients prone to excessive drinking. In patients one to both petit and grand mal epilepsy mepro-mate may precipitate grand mal attacks. Pre-ibe cautiously and in small quantities to patients with suicidal tendencies.

Side Effects: Overstimulation of the central nervous system, jitteriness and insomnia or drowsiness. Dextro-amphetamine sulfate: Insomnia, excitability, and increased motor activity are common and ordinarily mild side effects. Confusion, anxiety, aggressiveness, increased libido, and hallucinations have also been observed, especially in mentally ill patients. Rebound fatigue and depression may follow central stimulation. Other effects may include dry mouth, anorexia, nausea, vomiting, diarrhea, and increased cardiovascular reactivity.

Meprobamate: Drowsiness may occur and can be associated with ataxia; the symptom can usually be controlled by decreasing the dose, or by concomitant administration of central stimulants. Allergic or idiosyncratic reactions: maculopapular rash, acute nonthrombocytopenic purpura with petechiae, ecchymoses, peripheral edema and fever, transient leukopenia. A case of fatal bullous dermatitis, following administration of meprobamate and prednisolone, has been reported. Hypersensitivity has produced fever, fainting spells, angioneurotic edema, bronchial spasms, hypotensive crises (1 fatal case), anuria, stomatitis, proctitis (1 case), anaphylaxis, agranulocytosis and thrombocytopenic purpura, and a fatal instance of aplastic anemia, but only when other drugs known to elicit these conditions were given concomitantly. Fast EEG activity, usually after excessive dosage. Impairment of visual accommodation. Massive overdosage may produce drowsiness, lethargy, stupor, ataxia, coma, shock, vasomotor and respiratory collapse.

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Pearl River, New York

381-8



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Por una módica prima mensual —menos de lo que gasta en cosas menos importantes que la salud— usted se protege y protege a los suyos. La Triple S le ofrece servicios médicos, de hospitalización y dentales.

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SSS

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dominio efectivo de la tos, sin codeína

Cheracol D con dextrometorfano:

- acción antitusiva igual que con codeína, pero sin efectos secundarios narcóticos indeseables
- afloja las secreciones bronquiales
- refresca y suaviza la garganta
- tiene un agradable sabor a cerezas que lo hace muy popular entre los niños
- puede ser administrado a niños menores de dos años, bajo la vigilancia del médico

Cada onza fluida contiene:

Bromhidrato de dextrometorfano	9/10 gr. (60 mg.)
Cloroformo*	2 grs.
Guayacolato de Glicerilo	1⅔ grs.
Cloruro de Amonio	8 grs.
Tartrato de Antimonio y Potasio	1/12 gr.
Alcohol	3%

con corteza de pino blanco y de cerezo silvestre

*Cierta pérdida de cloroformo es inevitable.

Presentación: en frascos de 2 y 4 onzas.

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Whenever anxiety induces or intensifies clinical symptoms

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(chlordiazepoxide HCl)

Quickly relieves anxiety~Helps improve response in psychophysiologic disorders~Seldom impairs mental acuity or physical coordination, on proper dosage~Has wide margin of safety

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in instances by proper dosage adjustmen also occasionally observed at the lowe ranges. In a few instances syncope ha reported. Also encountered are isolat stances of skin eruptions, edema, mit strual irregularities, nausea and const extrapyramidal symptoms, increased creased libido—all infrequent and ger controlled with dosage reduction; cha EEG patterns (low-voltage fast activi appear during and after treatment; b crasias (including agranulocytosis), j and hepatic dysfunction have been re occasionally, making periodic blood and liver function tests advisable dur tracted therapy.

Usual Daily Dosage: Individualize mum beneficial effects. *Oral*—Adults and moderate anxiety and tension, 5 t.i.d. or q.i.d.; severe states, 20 or 25 or q.i.d. Geriatric patients: 5 mg b.i. q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxi Capsules, 5 mg, 10 mg and 25 mg—b 50. Libritabs™ (chlordiazepoxide) 5 mg, 10 mg and 25 mg—bottles of 1 respect to clinical activity, capsules ar are indistinguishable.

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EDICION DEL DEPARTAMENTO DE MEDICINA
ESCUELA DE MEDICINA - U. P. R.

DISPLAY SURVEYS

BOLETIN

ASOCIACION MEDICA DE PUERTO RICO

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21 MAR 1969

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EDITORIAL 509
Histoplasmosis in Puerto Rico

VOL. 60 OCTUBRE, 1968 NUM. 10

Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

UNA PINTA DE SANGRE NO PROPORCIONA MAS HIERRO

QUE UNA AMPULA DE 5 cc. DE



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

LAKESIDE

PRODUCTOS PARA PACIENTES QUE UD. VE A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

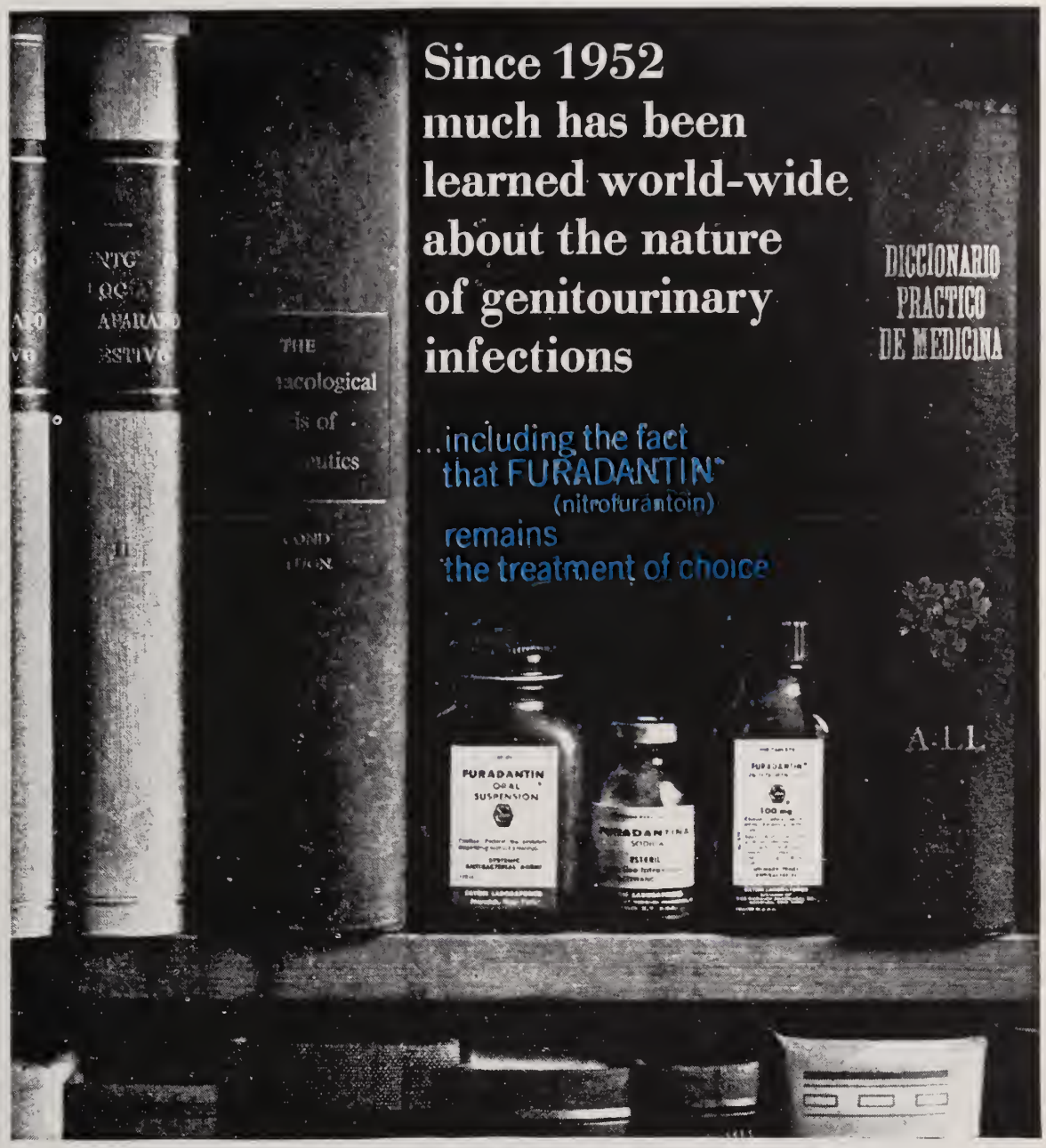
ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.



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in all degrees of cardiac edema

you can start with Lasix®
(furosemide)





Because Lasix starts to relieve edema promptly...helps you to maintain patients edema-free with more precise control than with thiazides.

Because Lasix's action is prompt and of comparatively short duration, you can evaluate patient response and make any necessary dosage adjustments more quickly than with longer-acting diuretics. You also spare patients the inconvenience of prolonged diuresis.

Because of its wide range of efficacy, Lasix can be used in all degrees of cardiac edema. Mild cardiac edema can usually be relieved with low, once-daily doses of Lasix—or an intermittent dosage schedule may be used. In more severe edemas, higher doses provide appropriate response. (A maximum daily dose of 200 mg. should not be exceeded; and it should be kept in mind that, as with thiazides, some patients may experience profuse diuresis at lower doses.)

These advantages of Lasix have been demonstrated in clinical practice in almost all countries in the Western World.* In England, and in many other countries, it is the most widely prescribed diuretic.

*Since introduction in this country prescription surveys indicate that an estimate of over 500,000 patients have been treated with Lasix.

step beyond
the thiazides

Lasix®
(furosemide)

Please see prescribing information which follows...

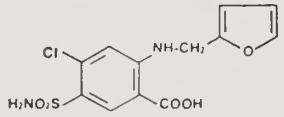
For most patients with cardiac edema... the response you want by selecting the dosage they need.

Lasix®
brand of furosemide

WARNING—Lasix (furosemide) is a new, potent diuretic, which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Lasix (furosemide) is a new diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by: a high degree of efficacy; a rapid onset of action; a comparatively short duration of action; a ratio of minimum to maximum effective dose higher than 1:10; the fact that it acts not only at the proximal and distal tubule but also at the ascending limb of Henle's loop.

Chemistry—Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The structural formula is as follows:



Indications—Lasix (furosemide) is indicated for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix (furosemide) is particularly useful when an agent with greater diuretic potential than those commonly employed is desired. Until further clinical experience is accumulated, Lasix (furosemide) is not recommended for use in hypertension.

Contraindications—Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound. Until further experience in children is accumulated, therapy with Lasix (furosemide) should be avoided.

Supplementary Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids. Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter and abnormalities corrected or the drug temporarily withdrawn. **In patients with hepatic cirrhosis and ascites initiation of therapy with Lasix (furosemide) is best carried out in the hospital.** Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. As with any new drug, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical. There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred. Based on a large survey of physicians and hospitals, both American and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.

Usage in Pregnancy—The use of any drug in pregnancy, lactation or in the childbearing age group requires that the potential benefits of the drug be weighed against possible hazards to the mother and child. Reproduction studies with Lasix (furosemide) in mice, rabbits, and rats have produced no evidence of drug-induced fetal abnormalities. However, Lasix (furosemide) has had only limited use in pregnant patients.

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix (furosemide) is administered, since Lasix (furosemide) potentiates the hypotensive effect of antihypertensive medications. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration which should be avoided, particularly in patients with renal insufficiency. Although no pronounced effect on carbohydrate metabolism has been demonstrated, periodic checks on urine and blood glucose should be made in diabetic patients receiving Lasix (furosemide). Occasional increases in blood glucose have occurred during therapy with Lasix (furosemide). Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Infrequent skin rash, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea, may occur. A single case of thrombocytopenia has been reported in which Lasix (furosemide) was considered to be the causative agent. There have been a few instances of leukopenia and one report of acute pancreatitis although relationship to the drug has not been established. Lasix (furosemide) induced diuresis has occasionally been accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, and urinary frequency.

Dosage and Administration—The usual dose of Lasix (furosemide) is 1 to 2 tablets (40 to 80 mg.) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg.) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg.) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). Based on completed studies, a maximum daily dose of 200 mg. should not be exceeded. Higher doses are currently under investigation. The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg./day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

How Supplied—Lasix (furosemide) is supplied as white, monogrammed, scored tablets of 40 mg. in amber bottles of 100.

HOECHST
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Cincinnati, Ohio 45229

16467

A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

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wear a snakeskin round one's head.



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May be habit forming), Phenacetin gr. 2 1/2,
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Keeps the promise of pain relief

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New

Therapeutic breakthrough in non-narcotic control of the pain of trigeminal neuralgia

Tegretol®
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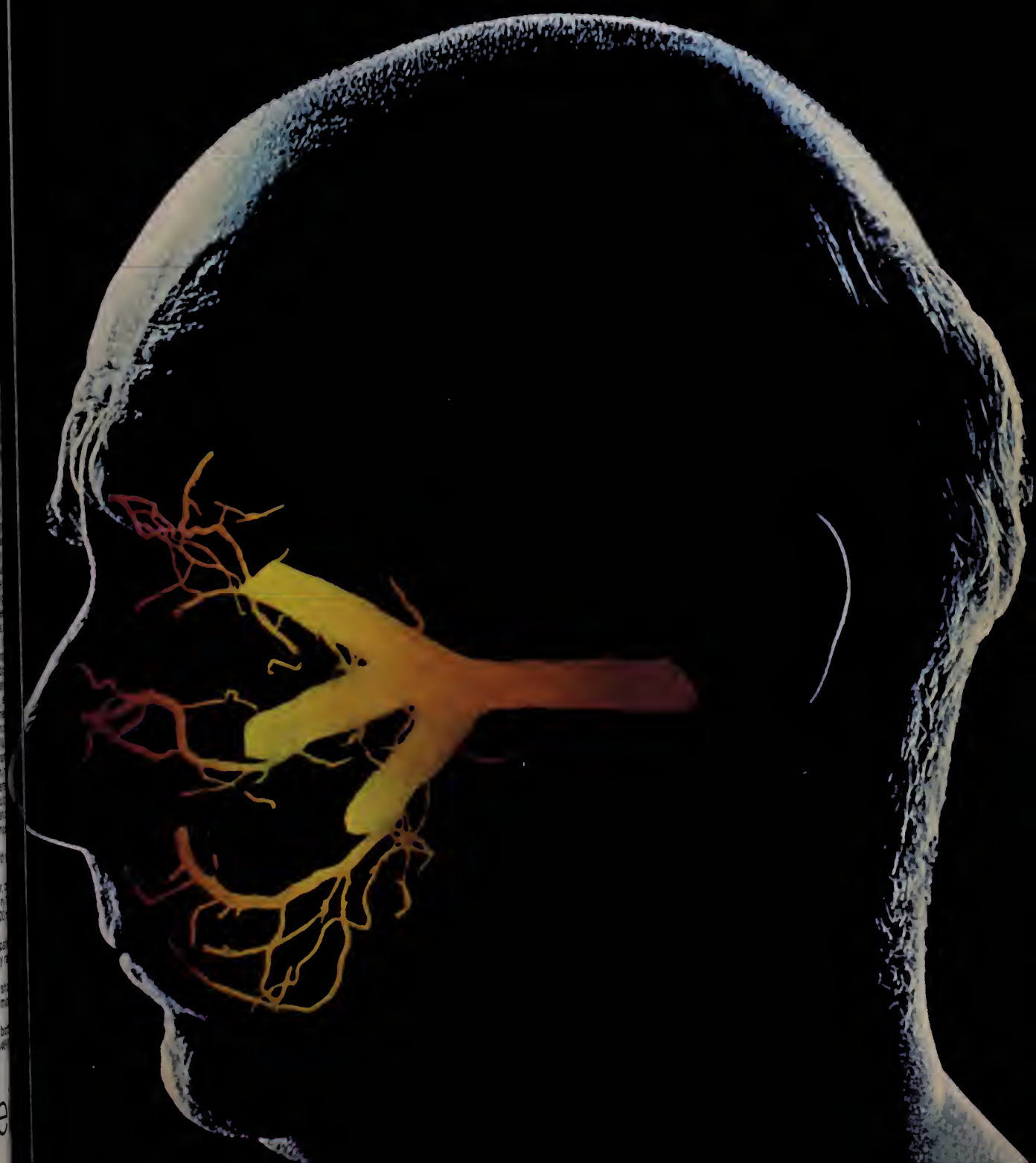
Warning
Fatal cases of aplastic anemia have been reported following treatment with Tegretol. Agranulocytosis, thrombocytopenia and transitory leukopenia have also been observed.
Complete blood and platelet counts should be done prior to and at regular intervals during treatment with the drug (see recommendations under "Important Note and Precautions") to help in the early detection of serious bone marrow injury. Abnormalities in initial blood tests should rule out use of the drug. Also, patients should be made aware of such early toxic signs of a potential hematologic problem as fever, sore throat, mouth ulcers, easy bruising and petechial or purpuric hemorrhage. Should such signs appear, the patient should be advised to discontinue the drug and to report to the physician immediately.

Indication Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia. It is not a simple analgesic and should never be administered for relief of trivial facial aches or pains.
Contraindication Do not use in those with a known sensitivity to any tricyclic compound or in those being treated with M.A.O.I. agents. As long a period as possible should elapse before using Tegretol in patients who have been treated with M.A.O.I.'s, with a minimum of 7 days. In such cases, initial dosage should be low and the patient's reaction to gradual increments closely observed.
Important Note and Precautions Familiarity with the clinical symptoms which lead to an accurate diagnosis of true trigeminal neuralgia and with the complete prescribing information, careful patient selection, a thorough examination before treatment and close patient supervision throughout the treatment period are essential to the safe and effective use of this drug.
Where feasible, Tegretol should not be used in conjunction with any potent drug which may increase the possibility of toxic reactions.
In pregnancy, the drug should not be prescribed during the first trimester and thereafter only to patients in whom the clinical situation warrants the potential risk. It should not be administered to nursing mothers.
Patients with increased intraocular pressure should be closely observed during treatment with this drug because of its anticholinergic effect.
Because of the drug's relationship to other tricyclic compounds, the possibility of activation of latent psychosis and, in the elderly, of confusion or agitation, should be considered.
Dizziness and drowsiness may occur and patients should be cautioned about the hazards of operating machinery or automobiles and of engaging in other hazardous tasks.
Use cautiously in patients with a history of coronary artery disease, organic heart disease, congestive failure or liver disease.
Before initiating therapy, the following laboratory procedures should be performed:
1. Complete blood and platelet counts which, if abnormal, should rule out the use of the drug.
2. Baseline evaluations of liver function.
During treatment with Tegretol, the following laboratory procedures should be performed:
1. Complete blood and platelet counts should be done at intervals of one week during the first month of drug treatment, every two weeks during the second and third months, and at monthly intervals thereafter for as long as the patient is taking the drug. A trend toward a decreasing white blood cell count should suggest a dosage reduction and more frequent laboratory and clinical evaluations. Should this trend continue, the dru should be discontinued.
2. Liver function tests must be performed at regular intervals during tre ment with this drug since liver damage may occur during therapy. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.
3. Periodic eye examinations, including slit-lamp, funduscopy and tonom etry, are recommended for patients being treated with this drug since many phenothiazines and related drugs have been shown to cause eye changes.
4. Complete urinalysis and BUN should be done on patients treated wi Tegretol because of observed renal dysfunction.
Adverse Reactions Dizziness, drowsiness, unsteadiness on the feet, nausea, vomiting, aplastic anemia, transitory leukopenia, agranulocytos eosinophilia, leukocytosis, thrombocytopenia, purpura, abnormalities in liver function tests, cholestatic and hepatocellular jaundice, urinary frequency, acute urinary retention, oliguria with elevated blood pressure, albuminuria, glycosuria, elevated BUN, microscopic deposits in the urin impotence, disturbances of coordination, confusion, headache, fatigue, blurred vision, transient diplopia and oculomotor disturbances, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, nystagmus, tinnitus, paralysis and other symptoms of cerebral arterial insufficiency, pruritic and erythematous rashes, urticaria, Stevens-Johnson syndrome, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, alopecia, diaphoresis, recurrence of thrombophlebitis, erythi multiforme and nodosum, aggravation of disseminated lupus erythematosus, gastric distress, abdominal pain, diarrhea, constipation, anorexia dryness of the mouth and pharynx, glossitis, stomatitis, fever, chills, adenopathy, lymphadenopathy, aching joints and muscles, leg cramps, conjunctivitis, left ventricular failure, aggravation of hypertension, hypotension, syncope and collapse, edema, aggravation of coronary artery disease and congestive heart failure. (Whether these cardiovascular effe are drug-related is not known. However, some of these complications h resulted in fatalities.) The necessity for discontinuing the drug should be dictated by the gravity and severity of the adverse reactions.
Dosage and Administration The drug should always be taken with meals if possible.
Initial: One-half tablet (100 mg.) b.i.d. on the first day. Thereafter, the do should be increased in one-half tablet (100 mg.) increments every 12 ho until freedom from pain is achieved. To relieve pain, between 200 mg. an 1200 mg. per 24 hours may be necessary.
Maintenance: Initial control of pain can be maintained in most patients with a dose of 400 mg. to 800 mg. daily. Maintenance doses may range between 200 mg. and 1200 mg. daily.
At least once every 3 months during treatment period attempts should be made to discontinue the drug or to reduce the dose to the minimum effective level.
Availability Round, white, single-scored tablets of 200 mg. in bottles of 100 and 1000. (B)46-820-A
For complete details, please see Prescribing Information.

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The loss of marital compatibility results in nearly 500,000 U.S. divorces each year.

Depression characterized by untold guilt feelings, grief and loneliness may follow.

When you diagnose depression, Tofrānil may be indicated for relief.

As maintenance therapy during the active phase of depression, Tofrānil can often help prevent relapse.

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated. In patients with cardiovascular disease, thyroid disorders, increased intraocular pressure; in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication or antihypertensive adrenergic neuron-blocking agents; and in those in their first trimester of pregnancy–the special precautions listed in the Prescribing Information should be carefully observed.

Toxic reactions severe enough to require discontinuation of Tofrānil are uncommon. However, for complete details, please refer to the complete Prescribing Information.

Turn page for brief summary of Prescribing Information.

in depression

Tofrānil® imipramine hydrochloride
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in depression





Tofrānil® Geigy

imipramine
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Tofrānil®, imipramine hydrochloride
Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy. Cardiovascular complications, Including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy. Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses. Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed. Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)R-46-850-C

For complete details, please refer to the full Prescribing Information.

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ASOCIACION MEDICA DE PUERTO RICO

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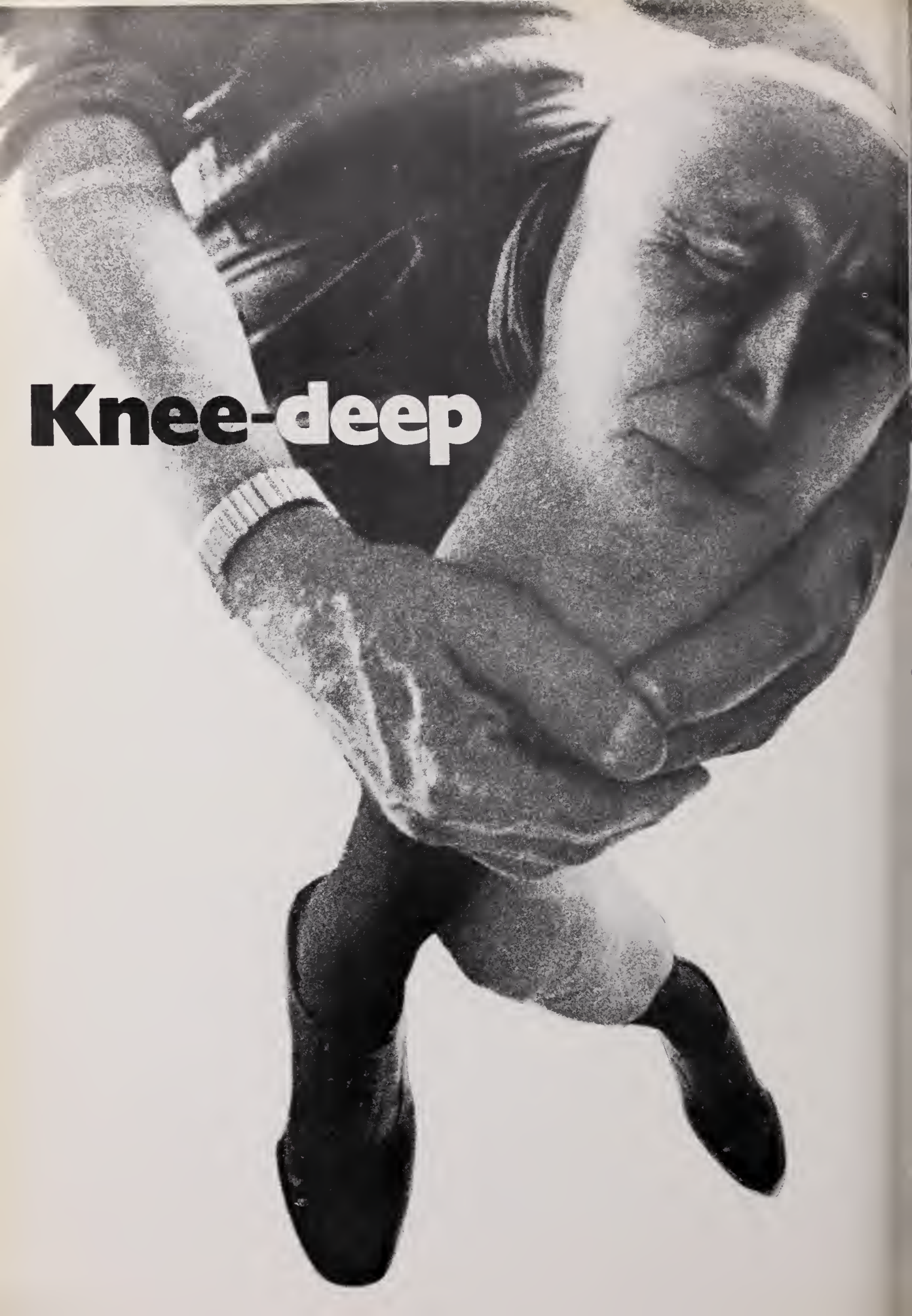
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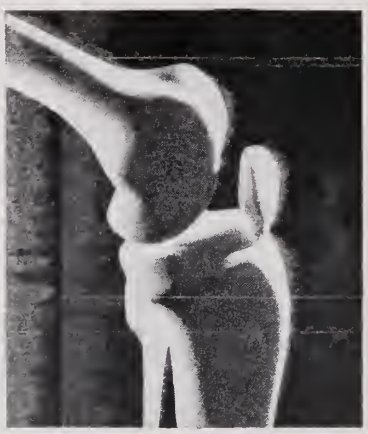
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For osteoarthritic knees, spines, shoulders, hips, etc.:

Tandearil®
oxyphenbutazone

Tandearil, oxyphenbutazone:
For brief summary see next page.

Geigy



Tandearil®
oxyphenbutazone

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily.

In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

(B)R-46-800-A

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PINTA IN PUERTO RICO

Arturo L. Carrión, MD

Pinta, carate, or mal del pinto, is a chronic, essentially cutaneous spirochetosis, characterized clinically by mildly inflammatory and dischromic changes which often lead to complete loss of pigment in situ. The disease is known to exist sporadically in various regions of tropical America and appears to be specially prevalent in Colombia, Venezuela, and certain parts of Mexico. A review of the literature on the subject shows a large number of publications, some of them dating back to the latter part of the 19th century. However, the etiology of the infection remained in obscurity for many years. Prior to 1938 the spirochetal nature of pinta had been suspected by Menck (1), González-Herrejón and Pallares (2), Howard Fox (3), and Pardo-Castelló (4), but it was not until that year that Grau-Triana and Alfonso-Armenteros, of Havana, were able to demonstrate the presence of authentic spirochetes in the lymph of scraped pinta lesions. The discovery was published by Sáenz *et al* (5, 6).

For a long time the writer had suspected the existence of pinta in Puerto Rico from the occasional finding of patients with symptoms suggestive of that disease. But in the absence of a specific diagnostic test, our suspicion could never be confirmed. However, shortly after the spirochetal nature of the disease became known, it was not difficult to find the infecting organism in the skin lesions of a clinically suspicious patient who attended the dispensary at the old School of Tropical Medicine in San Juan. A preliminary report on the subject was published in 1941 (7).

The present communication includes 3 additional cases of pinta and offers a more complete and graphic representation of this dermatosis as it actually occurs in Puerto Rico. For the sake of brevity only the first case will be presented in its entirety. Since the other 2 were similar to the above in most respects, their presentation will be limited to short dermatological descriptions with graphic illustrations of the patients' lesions and the demonstration of the infecting spirochetes.

Case Report

Case 1:

A colored, married, male, aged 42 years, an office employee in his home town of Vega Alta, Puerto Rico, is admitted to the University Hospital in San Juan, on December 8, 1942, complaining of discoloration, achromia and scaling of the skin on the left hand and wrist, left foot and perianal region.

According to the patient, infection started with a small area of inflammation on the tip of the left thumb, where the skin became scaly and vio-

From the Department of Dermatology, School of Medicine, University of Puerto Rico.

The observations recorded in this report were made by the author in the early '40s during the course of his activities at the old School of Tropical Medicine of the University of Puerto Rico under the auspices of Columbia University.



Fig. 1: (Case 1) - Palm of left hand showing complete loss of pigment, diffuse hyperkeratosis with minute pitting, and areas of scaling dermatitis; wrist with superficial inflammation, dischromic changes and exaggeration of lines of cleavage. Normal right hand shown for comparison.



Fig. 2: (Case 1) - Dorsum of left hand: the skin superficially inflamed, slate-colored pigmentation, achromic areas and scaling.

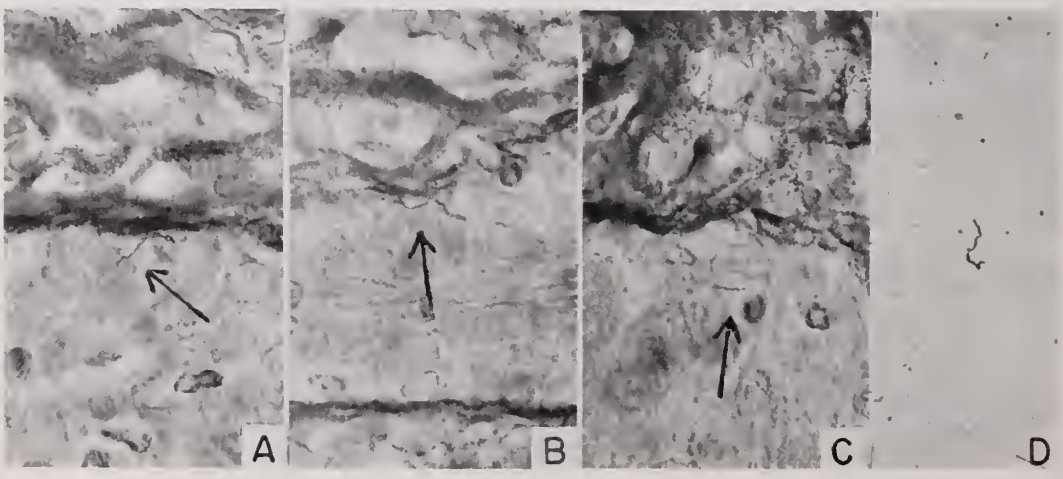


Fig. 3: (Case 1) - Biopsy sections showing spirochetes in the rete mucosum at A, B and C (Krajian silver impregnation technique). At D a spirochete in smear from exudate of scraped lesion (Wright stain, X 1400).

laceous. The pathologic process spread slowly but steadily with the development of satellite lesions, which later coalesced until the skin of the whole hand was affected. In the meantime similar, though less extensive lesions made their appearance on the left foot and perianal region. It was further noted by the patient that some areas within the infected skin would gradually lose their pigment until complete achromia was produced.

The past history revealed two attacks of gonorrhea 16 and 20 years ago, respectively; and a penile lesion 20 years ago which was cauterized by a local physician who gave him, in addition, 12 bismuth injections. The lesion disappeared in 2 weeks.

The palmar aspect of the left hand and fingers showed complete loss of pigment and diffuse hyperkeratosis (See Fig. 1). Within this area there were numerous discrete or confluent, variously sized patches of active dermatitis covered with laminated scales and, over the rest of the thickened epidermis, many minute depressions could be noted.

Around the wrist and on the dorsal aspect of the hand and fingers there was slight superficial inflammation (Figs. 1 and 2). On these areas the skin showed a characteristic dark-bluish to slate-colored pigmentation, some scaling, multiple foci of achromia and marked exaggeration of the lines of cleavage.

Similar, though not nearly as extensive changes were noted on the outer border of the left foot and perianal region.

A careful physical examination and roentgenologic studies of the heart and aorta, did not reveal other health abnormalities except as noted above.

The blood count, urine, feces and spinal fluid were normal, but the blood Wasserman showed a 3+ reaction and the Kahn test was 4+ . Dark-field examination of lymph obtained by superficial scraping of active lesions revealed the presence of numerous unequivocal spirochetes, and stained smears of the same material (Wright stain) also showed an abundance of the organism (Fig. 3, D).

Biopsy from the border of the lesion on the left hand was reported as follows: On one end of the section the stratum corneum is broad and well keratinized; the stratum granulosum is well developed; the rete mucosum is slightly thickened, and the dermal papillae are inconspicuous. The picture is entirely different on the other end of the section. Here the stratum corneum is thin, pale and loosely laminated; the stratum granulosum is not well defined and, in certain points, contains practically no granules; the rete mucosum appears much thinner and there are areas where the cytoplasm of the cells is vacuolated and the nuclei are irregular and pale. In addition, there is a small amount of melanin pigment scattered throughout this layer; the basal cell layer is inconspicuous and there is complete loss of pigment in some areas. The dermal papillae, which are broader and shallower than normal, show pallor and irregularity of the collagen bundles and, in places, there is lymphocytic infiltration about the blood vessels, with many of the lymphocytes showing pyknotic nuclei. A greenish yellow pigment is also noted here and there over the superficial portion of the dermis.

Under Krajian silver impregnation, numerous spirochetes may be observed in the Malpighian layer (Fig. 3). They are found in almost every microscopic field, varying from one to 6 or 8 per field, and are seen at different levels since the section is probably 8 to 10 microns thick. Some of the organisms are quite long, but it is impossible to be sure that two of these spirochetes are not joined together end to end. The turns are well defined and sometimes fairly sharp. No organisms are encountered in the derma or in the stratum corneum.

On December 18, 1942 the patient was discharged and referred for treatment to the out-patient clinic. He was given 10 intravenous weekly doses of neoarsphenamine, and these were followed by a series of 15 injections of bismuth. On his discharge from the O.P.D. six months later the skin lesions were remarkably improved.

After discharge the patient has been examined twice, in 1960 and 1965. There was no evidence of infection. The infiltration and discoloration of the skin had completely disappeared and so had the achromia except for a small area on the dorsum of the second and fourth fingers respectively. There was no complaint of any sort and the general condition was excellent.

Case 2:

A healthy-looking, well developed, colored male, 33 years old, was examined at the penitentiary in Río Piedras about 1943. He complained of a skin eruption affecting both hands and wrists, about 2 years duration; there were no subjective symptoms.

The patient stated that the disease had started on the inner border of the right hand as a small, slowly growing, whitish papule. This was followed

by the progressive development of other lesions throughout the adjacent skin until the whole palmar aspect of the hand and fingers became diffusely involved. Finally, a similar and symmetrically disposed eruption was gradually produced on the left hand and wrist.

The anterior aspect of the right hand (Fig. 4) showed extensive and irregular areas of achromia and hyperkeratosis with minute superficial pitting. Upon this background there was an eruption of flat, slightly raised, slate-colored to greyish papular lesions, mostly about 5 mm in diameter each, best noticeable on the thenar and hypothenar eminences. Dorsally (Fig. 5), the skin of the hand showed a slight but definite and diffuse infiltration, a slate-bluish discoloration, and a few small foci of achromia.

The skin changes on the left palm and wrist (Fig. 6) were not nearly as pronounced as those of the right hand.

The histopathologic picture was similar to that noted in Case 1. Dark field and stained preparations contained unequivocal spirochetes (Fig. 7), and the blood serology was strongly positive.

Treatment was conducted on the same principles followed in Case 1 - neoarsphenamine and bismuth series. At the time of discharge the skin lesions were practically healed but the achromic areas had not disappeared. The patient did not return for the follow-up observation.



Fig. 4: (Case 2) - Anteriorly the right hand showed extensive and irregular areas of achromia, and diffuse hyperkeratosis with superficial pitting. Upon this background, and best noticeable on the thenar and hypothenar eminences, there was an eruption of flat, slightly raised, slate-colored papular lesions.



Fig. 5: (Case 2) - Dorsally the skin of the right hand showed slight, but definite and diffuse infiltration, a slate-bluish discoloration and a few small foci of achromia.



Fig. 6: (Case 2) - The skin changes on the left palm and wrist were not nearly as pronounced as those of the right hand.



Fig. 7: (Case 2) - Unequivocal spirochetes in lymph from scraped lesions (Wright stain, X 1400)

Case 3:

A healthy-looking, well developed, colored, female, 42 years old, a housewife is admitted to the University Hospital on March 21, 1945 complaining of mildly pruriginous skin eruption of the left hand and wrist, of about 3 years duration.

The infection started on the index finger, anteriorly, as a reddish, scaly, occasionally pruriginous papule. The lesion extended superficially outward and, in a month or so, new efflorescences started to appear in succession eventually invading the whole hand and wrist.

The anterior aspect of the hand (Fig. 8) showed marked and somewhat rugose hyperkeratosis; diffuse achromia, except for a few small areas of pigmentation; scaling and numerous pin-point sized superficial depressions.



Fig. 8: (Case 3) - The palmar changes were closely similar to those of cases 1 and 2, but here the invasion of the wrist was more conspicuous and characteristic.

The eruption extended upward over the wrist for about 2 inches covering its inner two thirds. At this location there was a mild but definite inflammatory reaction with marked exaggeration of the lines of cleavage, and quite characteristic pigmentary changes. Some areas were hypochromic, while others showed tones of brown and bluish-gray.

Discrete eruptive areas, symptomatically similar to the lesion on the wrist, could be noted on the back of the hand (Fig. 9), while the dorsum of the fingers, specially over the last two phalanges, showed cutaneous atrophy and almost complete achromia.

A biopsy specimen revealed tissue changes similar to those noted in Case 1; and typical spirochetes were present in dark field preparations and in stained smears of the lymph from scraped lesions.

In this case the infection was subjected to penicillin therapy — 20,000 units every 6 hours for 10 consecutive days — after which the patient was referred to the out-patient clinic for follow-up observation. Unfortunately she never came back.



Fig. 9: (Case 3) - On the dorsum of the hand there was a mild and diffuse inflammatory reaction, marked exaggeration of the lines of cleavage and characteristic dischromic changes.

Summary

The existence of pinta in Puerto Rico has been definitely confirmed with the presentation of 3 unequivocal infections. The clinical, histopathologic and etiologic aspects of the disease as noted in this Island have been described and graphically illustrated. It is worth noting that the distribution of lesions in the Puerto Rican patients was limited mostly to the hands and wrists. This feature is in common with many of the cases described in Cuba. Finally none of the Puerto Rican patients showed evidence of systemic involvement.

Resumen

Con los 3 casos inequívocos de mal del

pinto que acabamos de describir se confirma sin lugar a dudas la existencia de esa enfermedad en Puerto Rico. Hemos presentado gráficamente los caracteres clínicos e histopatológicos de la infección según la hemos visto en esta Isla, así como también la presencia de espiroquetas auténticas en el tejido cutáneo y en la linfa obtenida por el raspado de las lesiones pintosas. Es curioso notar que en nuestros casos la infección estuvo limitada casi exclusivamente a las manos y muñecas, lo cual coincide con muchas de las observaciones hechas en Cuba. Debe advertirse además que en ninguno de los pacientes puertorriqueños pudo comprobarse la propagación de la enfermedad a los órganos internos.

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HYPERCALCEMIA IN SARCOIDOSIS

José Gándara, MD
Julián Vázquez, MD
Lillian Haddock, MD, FACP

The incidence of hypercalcemia in sarcoidosis in the various series reported has varied from 1.3 to 63 percent (1, 2). In the largest series studied in Puerto Rico 64 subjects had serum calcium done, seven of which were elevated (3, 4).

It is the purpose of this publication to summarize the clinical findings in two cases with sarcoidosis and severe hypercalcemia whom we have followed in the past year. The pertinent literature and the present concepts regarding the pathogenesis of hypercalcemia in sarcoidosis are reviewed.

Case Reports

Case 1:

A 33-year old mulatto male patient was referred to our Emergency Room on December 1966 for evaluation of generalized malaise, nausea, abdominal pain and jaundice of recent onset. He gave history of losing 15 pounds in the past 3 months; moderate alcohol intake, and history of river bathing. He claimed that for the past 6 years he had noticed scattered nodular skin lesions over the face, back and upper extremities. He gave history of occasional morning nausea and headache and occasional burning sensation in the eyes; denied sandy feeling in the eyes, photophobia or increased lacrimation. He was anorectic, but denied vomiting, diarrhea, constipation, jaundice or gastrointestinal bleeding. He denied excessive dryness of the skin, weakness or muscle cramps. He had never had chest pain, productive cough, hemoptysis, dyspnea or contact with tuberculosis. There was no cardiac, genitourinary or neurological symptomatology. He complained of polyuria but he ascribed it to increased water intake.

The past medical history revealed that in 1965 he had a renal colic with passage of a black stone. The family history revealed a maternal aunt with diabetes and a paternal uncle with renal stones and heart disease.

The patient used to work in the staining process in a sweater factory. He had never been given vitamin D nor calcium pills.

Physical examination revealed a well developed mulatto male who was alert and cooperative. Blood pressure was 130/80 mm Hg, pulse rate 80/min., respiration 16/min., temperature 37° C and weight 121 pounds. He had flat elevated plaques on the face, trunk and upper extremities (Fig. 1). There was no conjunctival jaundice and the fundoscopic examination was normal. The chest was clear and the heart was normal. Examination of the abdomen revealed a palpable liver 8 cm. below the right costal margin, firm and non tender nor nodular; the spleen was palpable 2 cm. below the left costal margin. He had several small, palpable, non tender, rubbery lymph nodes at the supraclavicular, right epitrochlear and bilateral inguinal regions.

The laboratory studies showed a normal hemogram; several urinalysis revealed + 1 albuminuria, negative for glucose, specific gravity between 1.003 to 1.006, the sediment showed pyuria without hematuria and some calcium oxalate crystals. The urine culture was reported as having less than 300 colonies per ml. The stool examination and rectal biopsy werd negative for schistosomiasis, the VDRL was non-reactive, the serum electrolytes were nor-

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Figure 1: Skin lesions in Case 1 before and after treatment.

mal and coagulation studies done were normal. Several fasting blood sugars and a glucose tolerance test were normal. The P. P. D. (intermediate strength) was negative at 72 hours. The liver functions tests showed the bromsulphalein excretion test to be 20 percent retention in 45 minutes; SGOT between 16-44 units and SGPT between 31-50 units; the LDH was normal. The prothrombin time, total cholesterol and serum bilirubin were normal, the Hanger test was 3+ in 48 hours; total serum protein was 8.0 g /100 ml, with albumin of 3.9 g /100 ml, globulin 4.1 g /100 ml and the A/G ratio of 0.9; the serum protein electrophoresis showed albumin of 34.2 percent; $alpha_1$ globulin, 4.08 percent, $alpha_2$ globulin, 9.18 percent; beta, 15.3 percent and gamma, 37.3 percent. The renal function tests showed a blood urea nitrogen ranging from 26 to 30 mg/100 ml, the corrected creatinine clearance 44 ml/min/1.73 m^2 and the P. S. P. test showed 27.8 percent excretion in two hours. The uric acid was 8 mg/100 ml.

The patient was evaluated at the Dermatology Clinic where the skin lesions were thought to be compatible with lupus pernio. A skin biopsy (Fig. 2) was diagnostic of sarcoidal granuloma. The serum

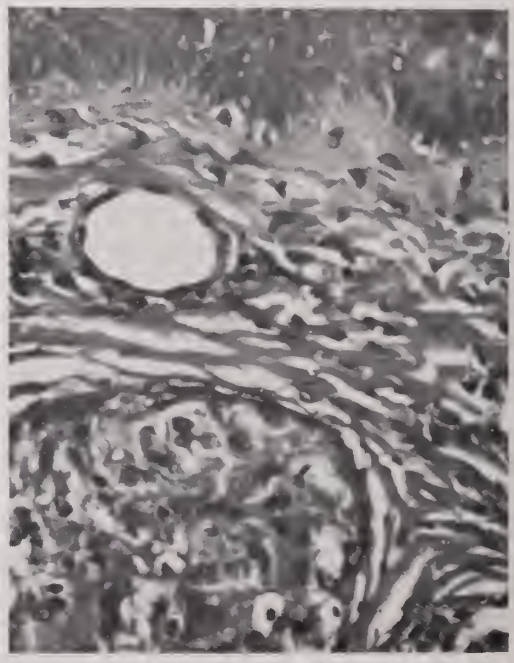


Figure 2: Sarcoidal granuloma in the skin (Case 1).

calcium were found to be repeatedly elevated, thus he was referred to the Endocrinology Clinic for further evaluation.

The calcium and phosphorus analysis were performed while the patient was on a constant low calcium (200 mg/day) and hydroxyproline restricted diet. The serum calcium ranged from 15.7 to 18.4 mg/100 ml, the serum phosphorus ranged from 3.0 to 4.4 mg/100 ml, and the alkaline phosphatase ranged from 31.4 to 40.5 SJR units. The alkaline phosphatase was also analyzed by the heat denaturation technique (at 56° C for 15 mins.) and the value was 16.5 SJR units. The diffusible calcium was 12 mg/100 ml, with a total serum calcium of 16.2 mg/100 ml. The urine calcium ranged from 391 to 569 mg/day; the urinary hydroxyproline ranged from 66 to 87 mg/day (normal 15-45 mg/day). The phosphate clearance was 14 ml/min. and the percentage of tubular reabsorption of phosphate was 68 percent.

Roentgenographic studies revealed bilateral, diffuse interstitial pulmonary fibrosis without visualized mediastinal lymphadenopathies and slight prominence of the main pulmonary artery (Fig. 3). Esophagogram, the upper gastrointestinal series and the gallbladder series were normal; the flat plate of the abdomen revealed bilateral renal calcific densities and hepatosplenomegaly; the intravenous pyelogram revealed bilateral nephrocalcinosis with delayed excretion in both kidneys. The bone survey showed diffuse demineralization of the bones of both hands (Fig. 4) and proximal tibiae.

The patient had a Kveim test done at the V. A. Hospital which was positive. Liver and lymph node biopsies showed granulomas compatible with sarcoidosis (Fig. 5).

Ophthalmological evaluation with the slit-lamp examination showed no evidence of band keratopathy. The electrocardiogram showed a shortened Q-T interval consistent with hypercalcemia.

Pulmonary function tests revealed a mild obstructive and restrictive respiratory dysfunction as shown by decrease in the vital capacity, inspiratory capacity and total lung capacity. There was arterial hypoxemia, as shown by an arterial O_2 saturation of 91 percent breathing at room air which was corrected to normal upon breathing 100 percent oxygen. The latter findings are compatible with an alveolo-capillary block.

On August 14, 1967 the patient was started on 40 mg of prednisone per day and Isoniazid® 300 mg daily. The skin lesions and lymphadenopathies

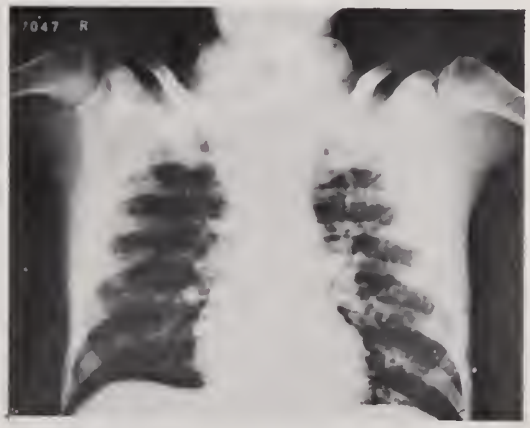


Figure 3: Pulmonary lesions in Case 1 (see text).



Figure 4: Diffuse demineralization of the bones of both hands in Case 1 (above). Increased mineralization of the bone structures of the hands in Case 1 after 11 months of therapy (below).



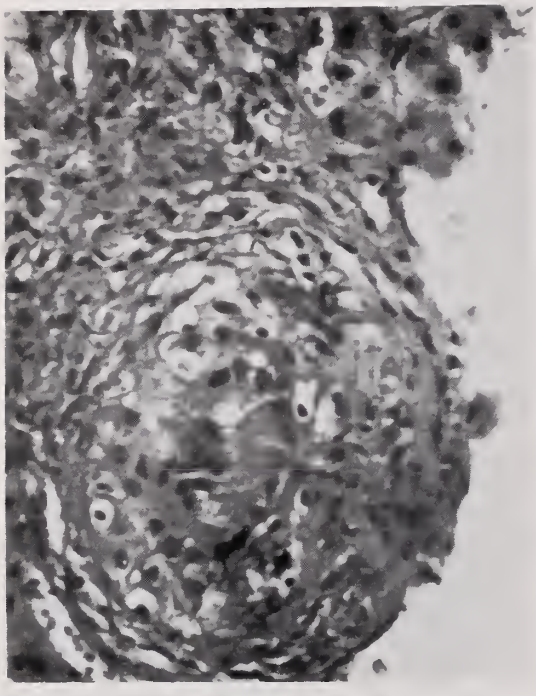


Figure 5: Sarcoidal granuloma in the liver (Case 1).

disappeared within two weeks of starting therapy. The serum calcium dropped to 10.5 mg/100 ml after 12 days of therapy and the urine calcium dropped to 144 mg/day by August 9, 1967, 25 days after treatment was started (Fig. 6). Prednisone was slowly tapered down to 5 mg daily, dose in which he is maintained at the present time. The serum calcium has been ranging between 9.9 and 11 mg/100 ml and the serum phosphorus between 3.3 to 4.4 mg/100 ml. The urinary hydroxyproline gradually decreased and on April 9, 1968 was 27 mg/day. The hepatosplenomegaly has not changed. Of interest are the changes in the transaminases. Upon starting treatment with prednisone the serum transaminases were as high as 106 units of SGOT and 500 units of SGPT on September 21. They gradually decreased and on his visit on June 10th the SGOT was 46 units and the SGPT was 74 units. The alkaline phosphatase has remained persistently elevated, the last determination on June 10th being 21.2 SJR units. The bilirubin, prothrombin time, Hanger's and thymol turbidity have remained normal. On June 8, 1968 the serum albumin was 4.95 g/100 ml and the serum globulin 3.55 g/100 ml. The renal function has shown improvement with a negative urinalysis, normal blood urea nitrogen, a normal uric acid and a corrected creatinine clearance was 85 ml/min/1.73 m^2 after 7 months of therapy. The patient is still passing painless, sandy urinary sediment.

The pulmonary status has remained unchanged after 7 months of therapy. The chest X-ray and the subsequent pulmonary function tests did not show any appreciable change.

In the 11 months of treatment the patient has gained 57 pounds in weight. A repeated glucose tolerance test was normal. The bone survey was repeated and revealed improvement of the demineralized bony structures in both hands.

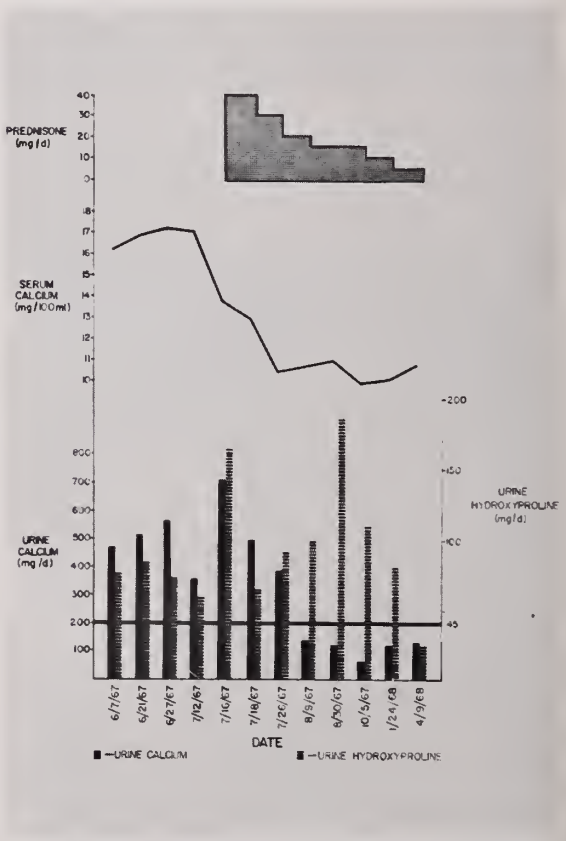


Figure 6: The effect of treatment with prednisone upon the serum calcium, urinary calcium and urinary hydroxyproline in Case 1. The horizontal line marks the upper limit of normal for both the urine calcium and the urinary hydroxyproline.

Case 2:

A 53-year old white male patient, brother of 3 sisters with polycystic kidneys, was seen in this hospital during 1966 for evaluation of renal status. In the checkup he had a chest X-ray which revealed diffuse pulmonary fibrosis. The pulmonary findings were not thought to be consistent with pulmonary tuberculosis. The patient failed to return to this hospital, but was being followed by a private physician. The latter interpreted the radiological findings as active pulmonary tuberculosis and started him on anti-tuberculous therapy. The patient reappeared for follow up with the above history and complaining that the lymphadenopathies he had noticed for several years had become more prominent.

He was completely asymptomatic except for 15 pounds weight loss in the past years. He denied any cardiopulmonary symptoms, headaches, constipation, anorexia, dryness of skin, cramps, polyuria, muscle weakness, photophobia, lacrimation or sandy feeling in the eyes. No history of contact with tuberculosis. No gastrointestinal or genitourinary complaints.

The past history is relevant in that he had passed several urinary stones 7 years before. The family history was non contributory.

Physical examination revealed a well developed white male patient in no distress and cooperative. Blood pressure 118/78 mm Hg, pulse 88/min., respiration 22/min., temperature 37°C and weight 121 pounds. The pertinent physical findings were generalized lymphadenopathy. Lymph nodes were freely movable and of rubbery consistency. He had a small (2 cm) lymph node in the right axilla and a large (6 x 3 cm) lymph node in the left axilla. The right lung field was clear, but in the left lung field there was diminution of breath sounds and respiratory ronchi in the left base with normal percussion and tactile notes. The heart was normal. The liver was palpable 2 cm below the right costal margin; the spleen was not palpable.

Laboratory studies revealed a normal hemogram except for a 15 and 20 percent eosinophilia. The stools were negative for parasites. The urinalysis showed traces of albumin, no glucose, specific gravity 1.013 and the sediment showed mild pyuria. The urine culture for predominant organism and acid fast bacilli were negative. The VDRL was non reactive, the PPD, battey and histoplasmin skin tests were negative after 72 hours. Serum electrolytes were normal. Liver function tests showed a total protein of 8.73 g/100 ml with albumin of 4.45 g/100 ml and globulin 4.38 g/100 ml. The serum protein electrophoresis showed albumin 43.9 percent, $alpha_1$ globulin, 3.7 percent, $alpha_2$ globulin, 7.4 percent; beta, 14.1 percent and gamma, 30.9 percent; the prothrombin time, Hanger's, transaminases, bilirubin, alkaline phosphatase and thymol turbidity were normal. The renal function tests revealed a blood urea nitrogen of 20 mg/100 ml; a 14 hour dehydration test showed normal concentration ability and the corrected creatinine clearance was 110 ml/min/1.73 m^2. The serum uric acid was 7.6 mg/100 ml.

The calcium and phosphorus determination were performed on a low calcium, hydroxyproline restricted diet. The serum calcium ranged from 12.2 mg to 13.6 mg/100 ml, the serum phosphorus ranged from 3.0 to 3.6 mg/100 ml. The urine calcium ranged from 196 mg to 444 mg/day and the urinary hydroxyproline ranged from 29.4 to 42 mg/day.

The roentgenological studies performed were a chest plate and chest tomogram which revealed bilateral fibrotic changes, more extensive in the left lung field and right lung base with an early calcific density in this right base. There was bullae formation in the left upper lobe and right lower lobe. No definite cavitation or hilar lymphadenopathies were found. The intravenous pyelogram, infusion pyelogram and skeletal survey were reported as normal.

The patient had a positive Kveim test and a biopsy of a cervical lymph node which revealed granuloma infiltration consistent with sarcoidosis.

The tubular maximum reabsorption of glucose, as a measure of parathyroid function was performed. The TmG/GFR value was 0.97 (normal 1.97 +0.10).

While the patient was hospitalized at the Nursing Home he had an episode of painless gross hematuria. A complete urological work up including cystoscopy and retrograde pyelogram were normal. A renogram done showed mild bilateral excretory defect which was not modified with hydration. The renal scanning showed bilateral hypofunctioning areas throughout both renal shadows.

Pulmonary function studies before therapy was given, revealed a restrictive pattern as shown by decrease in the inspiratory capacity, the vital capacity and total lung capacity. Arterial blood studies revealed mild hypoxemia as shown by an oxygen saturation of 93 percent which was corrected to 100 percent when breathing 100 percent oxygen.

On April 18, 1968 the patient was started on

prednisone 30mg daily and Isoniazid® 300 mg daily. Six days after treatment the serum calcium was 11 mg/100 ml and the serum phosphorus was 3.4 mg/100 ml. After eleven days of treatment the serum calcium was 10.2 mg/100 ml and the serum phosphorus was 2.3 mg/100 ml. The urine calcium ranged from 140 to 300 mg/day and the last determination after 6 weeks of therapy was 140 mg/day. The urine hydroxyproline has been normal averaging 30 mg/day. The eosinophilia has come down to 6 percent. The prednisone was slowly tapered down to 5 mg daily, dose in which he is maintained at the present time. The serum calcium has ranged from 9.9 to 10.7 mg/100 ml and the serum phosphorus has ranged from 2.3 to 2.7 mg/100 ml. The lymphadenopathies started to diminish in size within one week of therapy and at present they are almost imperceptible. The renal, liver and pulmonary status has been unaltered. The patient has gained 8 pounds since therapy was started and has remained asymptomatic.

Discussion

Alterations in calcium metabolism are among the most common metabolic derangements in sarcoidosis. These are manifested by hypercalcemia and or hypercalciuria, secondary to an increase in the gastrointestinal absorption of calcium, mediated by an altered sensitivity to vitamin D.

The first description of the association of hypercalcemia in sarcoidosis was made by Harrel and Fisher in 1939 (5). The reported frequency of this association has varied widely from series to series (see Table I). A mean 17 percent frequency was encountered by Mayock (7) and Taylor (10) in their analysis of the largest reported series.

No positive correlation has been encountered between the existence of hypercalcemia in sarcoidosis and such variables as age, sex, race, organs involved in the systemic process or bone involvement (2, 10, 13, 14, 15). An inconsistent correlation has been encountered with the stage of the disease. Some authors claim that in their experience hypercalcemia is more common in the chronic stage of the

TABLE I: INCIDENCE OF HYPERCALCEMIA IN SARCOIDOSIS

Authors and References		Total No. of Cases	Hypercalcemia	
			No.	*Percent*
Harrel	(5)	11	6	55
Israel	(1)	160	2	1.3
Longcope	(6)	23	6	27
McCort	(2)	16	10	63
Mayock	(7)	97	18	19
Labow	(8)	100	21	21
Cummings	(9)	113	40	35
Taylor	(10)	345	57	16.5
Bacharach	(11)	46	7	15
Putkonnen	(12)	60	2	3
Ramírez	(4)	64	7	10.9
Mean	(10, 7)			17

disease (13, 16) while others have found it more frequently in the subacute stage (15).

The incidence of hypercalciuria in the disease has varied from 15 to over 50 percent and in all series reported it is twice as frequent as hypercalcemia (12, 16). This may lead to a higher incidence of renal lithiasis (17), a concept which is not supported by the analysis of 306 of sarcoidosis by Murphy (18) in which he found an incidence of 1.3 percent, not different from that seen in the general population.

The pathogenesis of the changes in calcium metabolism in sarcoidosis started to be investigated shortly after the introduction of calciferol treatment for this condition. The rationale for the beneficial effect of calciferol or dihydrotachysterol on the sarcoidal granulomas was explained on the tendency to increase the phosphorus excretion, thereby decreasing the phosphorus content of the phospholipids in the tissue which is thought to be one of the causative factors in the production of the epithelioid tubercle of sarcoidosis (19). With the use of this therapy many of the patients with proven sarcoidosis showed extreme sensitivity to this modality of treatment, and this suggested that they were more prone to the toxic manifestations of vitamin D than normal individuals (20, 21, 22).

These observations led Henneman (23, 24) and Anderson (20) to independently investigate the alterations in calcium metabolism in patients with sarcoidosis associated with hypercalcemia and hypercalciuria. Balance studies demonstrated an increased gastrointestinal absorption of calcium and hypercalciuria which was greater than could be accounted for by an increased absorption alone. Since the calcium changes mimicked those seen in hypervitaminosis D, this led them to postulate that the hypercalcemia and hypercalciuria in sarcoidosis resulted from an increased gastrointestinal absorption of calcium similar to that seen in vitamin D intoxication or by an increased sensitivity to vitamin D. The latter has been favored since determination of the serum vitamin D levels in hypercalcemic sarcoid have been found to be either low or normal (25, 26, 27). Bell (26, 27) confirmed the observations made by Henneman and Anderson. Upon the administration of small doses of vitamin D to three sarcoid patients with hypercalciuria he showed a definite increase in the gastrointestinal absorption of calcium without altering the serum vitamin D level. The same dose of vitamin D given to normal individuals failed to bring about any changes in the calcium balance. He thus postulated that there was definitely an increase sensitivity to vitamin D in these subjects.

The demonstration by Taylor and his associates (10) of an increased incidence of hypercalcemia in patients with sarcoidosis during the summer months when the synthesis of vitamin D_3 from dihydrocholesterol in the skin is enhanced by ultraviolet radiation has added further strength to the postulate that there is an increased sensitivity to vitamin D in this disease.

Recently Norman and De Luca (28) and Avioli (29) have studied the metabolic fate of tritiated vitamin D_3 in animals and humans. They have shown that vitamin D_3 is rapidly converted in a series of metabolites, the most active of which has been denoted as peak IV, the chemical composition of which is still unidentified. They have shown that this metabolite is three to four times more active than vitamin D_3 when tested in the rachitic rat. Studies of the metabolic fate of tritiated vitamin D_3 being now conducted by Avioli's group (30) may throw some light in the possible alteration of vitamin D metabolism in sarcoidosis.

The presence of hypercalcemia and hypophosphatemia in the presence of renal insufficiency in Case 1 made us think of the pos-

sibility of concurrent primary hyperparathyroidism. Hypophosphatemia (12) has not infrequently been shown in sarcoidosis but whenever present we must exclude the possibility of primary hyperparathyroidism. There are several reports in the literature where unnecessary surgical explorations of the neck were performed, not revealing parathyroid pathology (20, 31). Up to the present time there are eleven cases reported with the proven diagnosis of both conditions in the same patient (32, 33, 34, 35). The differentiation is of utmost importance because of the excellent prognosis in hyperparathyroidism. The following studies can be helpful for ascribing the hypercalcemia to one of these distances.

The *cortisone test* has been the most acceptable procedure in differentiating one condition from the other. The hypocalcemic effect of cortisone is sarcoidosis was described in 1952 by Schulman and associates (36). Since then its use has been widely accepted. Cortisone or its derivatives, are used in oral dosage of 50 mg every 8 hours for 10 days (37). A positive response to steroids favors the possibility of sarcoidosis as an etiologic factor; exception to this fact are those cases of sarcoidosis which have not responded to the administered cortisone. Dent and co-workers (32) noticed that in one case which failed to respond to cortisone, they gave hydrocortisone preparation and the serum calcium became normal. They speculated that the liver involvement may prevent the adequate conversion of cortisone to the physiologically active hydrocortisone (32). The fact that the hypercalcemia in hyperparathyroidism is not affected by steroids is refutted by the reports where lowering of the serum calcium has been achieved by the use of cortisone (38, 39). This latter effect has been explained by the possible antagonism of steroids to parathyroid hormone (40). The mechanism of action of cortisone has been ascribed to different factors, the most accepted is the direct antagonism to vitamin D (13, 41). Avioli (42) has recently studied the metabolism of D_3 H^3 in normal subjects after the administration of cortisone. He showed a delayed appearance of D_3 H^3, a decrease half life and a rapid appearance of biologically inactive lipid soluble D_3 H^3 metabolites. This effect of cortisone on vitamin D_3 H^3 metabolism most likely accounts for its beneficial effect in sarcoidosis. In our two patients the use of prednisone was effective in reducing the serum calcium to normal.

In the differential diagnosis of the two conditions emphasis has been given to the level of the serum phosphorus, which has been described to be normal in sarcoidosis and low in primary hyperparathyroidism in the absence of renal insufficiency (43). It is accepted that parathyroid hormone produces phosphaturia and hence hypophosphatemia by depressing the net phosphorus reabsorption by the renal tubule. This is not pathognomonic of hyperparathyroidism since many other conditions, including sarcoidosis have shown an abnormal phosphorus excretion (44). Putkonen and associates (12) have reported that the low serum phosphate levels was by far more common than hypercalcemia in sarcoidosis. They claim that the low serum phosphate is related to the abundant synthesis of phospholipids by the granuloma of sarcoid. The evaluation of the phosphorus metabolism in sarcoidosis is furtherly complicated by the phosphaturic effect of steroids (45). In our two cases the serum phosphorus values had been in the low levels with an increase in the phosphate clearance and a diminished tubular reabsorption of phosphate. In Case 2 the hypophosphatemia was more accentuated when steroid therapy was instituted.

Another procedure which can be useful in the differentiation of both diseases is the maximal rate of tubular reabsorption of glucose (Tm G). This is expressed as Tm G/GFR

ratio for correction of any difference in the functioning nephrons if any renal damage is present (46). According to experimental data the reabsorption of glucose by the renal tubule may be a direct evidence of parathyroid function. Halver and associates in 1965 (47) studied thirty patients with one or both diseases and found that the ratio in normal individuals was 1.97 + 0.10; that in cases of hyperparathyroidism this ratio was above 2.0 and in hypoparathyroidism the ratio was below 1.70. In cases of hypercalcemia of non-parathyroid origin the values were similar to those of the hypoparathyroid group. Transbol (35) reported eight cases of hypercalcemic sarcoidosis and in two of them the Tm/GFR ratio was above 2.5 and subsequent neck surgery exploration revealed parathyroid tumor in both. The mechanism of action by which the parathyroid hormone may influence the tubular reabsorption of glucose is thought to be the inhibition of the tubular reabsorption of phosphate, which then makes the transport apparatus available for the tubular transport of glucose. A direct action of the hormone on the glucose reabsorption in the proximal tubules has also been postulated (46, 47). In Case 2 the Tm G/GFR ratio was low, consistent with a hypercalcemic state in which there is inhibition of parathyroid hormone.

Recently Reiss and associates (48) reported a highly sensitive, reproducible radioimmunoassay for parathyroid hormone. This has made possible a clear differentiation between normal, hyperparathyroid and hypoparathyroid human sera. The assay in the cases of hypercalcemic sarcoidosis showed unmeasurably low levels of parathyroid hormone. This level became normal after steroid therapy. This sensitive assay will solve the problems in cases where hyperparathyroidism is concomitantly present with sarcoidosis. The persistence of normocalcemia, while on a very low maintenance dose of prednisone in our cases speak against a concurrent primary hyperparathyroidism.

The excretion of urinary hydroxyproline in cases of sarcoidosis was reported recently by Massaro and coworkers (49). Hydroxyproline is a non essential amino acid that occurs almost exclusively in tissue collagen. The main organic constituent of bone is collagen, and bone collagen is the major source of urinary hydroxyproline. An elevation of urinary hydroxyproline has been found in metabolic bone diseases associated with either increased bone resorption or increased bone collagen synthesis (50, 51, 52).

Massaro found hydroxyprolinuria in 9 subjects who had had sarcoidosis for less than two years and who presented moderate lung fibrosis. In 8 subjects in whom the disease had been present for over 2 years and who showed only minimal pulmonary fibrosis the urinary hydroxyproline was normal. None of these subjects had hypercalcemia and no mention was made regarding skeletal involvement or the presence of hypercalciuria. The urinary hydroxyproline fell to normal in all subjects irrespective of treatment or without treatment. In all cases a fall in the urinary hydroxyproline was related to a fall in alkaline phosphatase concentration and clearing of the pulmonary lesions. They concluded that the determination of the urinary hydroxyproline is a more sensitive parameter and accurate index of the extent of the disease and its therapeutic or spontaneous alteration than are currently available techniques.

In the two cases herein reported both of which had had the disease for over two years only one had hydroxyprolinuria. In both cases the disease was active and both showed extensive pulmonary fibrosis. We would have expected hydroxyprolinuria in both cases were this a parameter of activity of the disease. The presence of hydroxyprolinuria in the one subject with bone involvement makes us postulate that the hydroxyprolinuria may be asso-

ciated with the bone disease. The hydroxyprolinuria in our case correlated with the hypercalciuria rather than with the hyperphosphatasia, the latter most likely due to the granulomatous involvement of the liver, rather than to the bone involvement as suggested by the heat denaturation test (53).

Although vitamin D has long been recognized as a nutritional factor essential for proper skeletal development, an additional effect of vitamin D on calcium homeostasis has been recognized, namely the mobilization of calcium from bone (54, 55, 56). In an altered sensitivity state to vitamin D as seen in sarcoidosis, the latter could be playing a role and if significant, hydroxyprolinuria would be expected. There is no available data to support this contention and further studies are warranted.

The elevation of the serum transaminases upon treatment, in Case 1 was rather impressive. Hepatic sarcoidosis may improve upon steroid therapy (57) or may progress to a fatal state (58). Improvement in the liver functions tests upon treatment is well recognized. In the articles published on hepatic sarcoidosis, none has recorded the serum transaminases and no reference was found in the literature regarding transaminase values in sarcoidosis. We can speculate that with healing of the granulomas which may either disappear or become fibrosed (57) the elevated transaminases may revert to normal.

Cortisone or its derivatives are the most effective and widely used treatment of hypercalcemia in sarcoidosis. The concomitant use of Isoniazid® is indicated because of the close relation between sarcoidosis and tuberculosis. Emphasis has been given to avoidance of excessive exposure to sunlight and ingestion of exogenous vitamin D (10).

Summary

The presence of hypercalcemia in two subjects with sarcoidosis has been reported. Besides hypercalcemia, they also presented hypercalciuria and in one subject hydroxyprolinuria and bone disease was evident. Reversal of these metabolic derangements was achieved with steroid therapy.

The present concepts regarding the pathogenesis of hypercalcemia in sarcoidosis are reviewed and the differential diagnosis between hypercalcemic sarcoidosis and primary hyperparathyroidism was discussed.

Resumen

Se informan dos casos de sarcoidosis que presentaron hipercalcemia. Además de hipercalcemia, estos enfermos presentaban hipercalciuria y uno de ellos demostró hidroxiprolinuria y cambios oseos. Los cambios metabólicos observados se normalizaron mediante la terapia con esteroides.

Se discuten los nuevos conceptos en relación a la patogenesis de hipercalcemia en sarcoidosis y se explicó el diagnóstico diferencial entre sarcoidosis con hipercalcemia y el hiperparatiroidismo primario.

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LACTIC AND MALIC DEHYDROGENASE ISOENZYMES IN HUMAN NORMAL AND MALIGNANT TISSUES

E. Conde del Pino, MS
A. A. Cintrón Rivera, MD
Luis A. Vallecillo, MD

Disease leads to a disturbance in the harmonious pattern of enzyme action. The degree of deviation in enzymatic activity can reflect biochemical lesions in the metabolic activity of diseased cells. Although histologic tissue examination remains the pivotal factor in the diagnosis of malignant neoplasia, there are diagnostic aspects in patients with malignancies in which biochemical examination of body tissues may supplement or extend information obtained from histological study.

The discovery of "isoenzymes", enzyme fractions with similar catalytic properties but with different electrophoretic mobilities or chromatographic characteristics (1, 2), has made possible the detection of specific patterns of abnormality of these enzymes in disease (3). The work of Okabe, *et al* (4) and Latner, *et al* (5) has shown that a change in the content of lactic dehydrogenase (LDH) isoenzymes may be one of the earliest alterations which is demonstrable soon after a tissue becomes malignant. These changes in the isoenzymes are observed before there is any change in the activity of the serum enzymes.

The present report deals with the lactic (LDH) and malic (MDH) dehydrogenase isoenzyme distribution in human adenocarcinoma of the stomach, adenocarcinoma of the sigmoid colon, epidermoid carcinoma of the lung and their tissues of origin.

Materials and Methods

Tissue weighing 500 mg to 1 g was obtained at surgery and immediately frozen in liquid nitrogen. Samples were kept at -20° C for not more than 24 hours prior to use. Neoplastic tissues were obtained from areas with little or no necrosis. All of the malignancies were primary tumors. Normal tissues were obtained from areas several centimeters away from the original neoplastic lesions. The morphological characteristics of the various tissues were ascertained by microscopic examination.

Extracts

Frozen specimens were quickly weighed, washed 3 times in ice-cold saline, drained on filter paper, suspended in 1 to 2 parts (W/V) of cold physiological saline and homogenized in an all-glass Potter-Elvejhem homogenizer. The homogenates were centrifuged at 2,000 x g for 10 minutes and the supernatants were assayed immediately.

Separation and visualization of LDH and MDH isoenzymes

Electrophoresis on cellulose acetate was performed

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by Kohn's method (6) using Seprahore III strips * and 15-30 ul of undiluted samples. To compare mobilities both tumor and normal samples were run on the same strip. The visualization of the separated LDH isoenzymes was accomplished using Barnett's method (7). The incubation medium for MDH was that of Goldberg (8). Strips were fixed in 5 percent acetic acid. Fractions were numbered from the anode toward the cathode (Fig. 1). The strips were scanned in a Canalco Model E microdensitometer **.

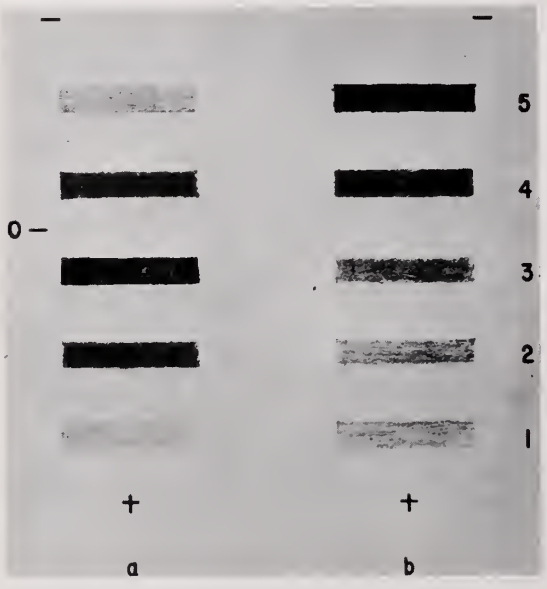


Fig. 1: Illustrative representation of LDH isoenzymes separated by cellulose acetate electrophoresis. a, normal tissue, b, malignant tissue, O represents the origin.

Results

Lactic dehydrogenase (LDH)

Normal and malignant tissues under study contained 5 LDH isoenzymes irrespective of site or origin of the tumors. In general, neoplastic tissue showed a marked shift towards the slow moving isoenzymes when compared to the normal tissues (Table I, Fig. 1). Comparison of the electrophoretic mobility of the isoenzymes from the neoplasms and the corresponding normal tissues evidenced no differences and supernumerary fractions were not obtained from the tissues examined.

Malic dehydrogenases (MDH)

All of the samples tested revealed only two MDH isoenzymes. The first one, (MDH_1), moving towards the anode, is of cytoplasmic origin whereas the second one (MDH_2), cathodic in character, is of mitochondrial origin (9). Comparison of the malignant and the corresponding normal tissues evidenced almost no variation in the relative concentrations of the two fractions (Table 2). Mobility differences were not found.

Discussion

Many current enzymologists state that all intracellular enzymes are built into a specific and precise structure and that their function depends to a large extent on organization. Thus, many studies have been undertaken in the hope of finding specific alterations in metabolism associated with neoplastic change. Extensive studies have not revealed any such qualitative change. However, tumors often show quantitative differences from the parent tissues (10, 11). Our data shows that the malignant tissues under study have an increase in the relative concentrations of the cathodic moving LDH isoenzymes when compared with their corresponding normal tissues. The finding of such a pattern may be of value in determining the presence of a malignancy particularly since, as shown by Langvad (12), the change in the LDH isoenzyme pattern is de-

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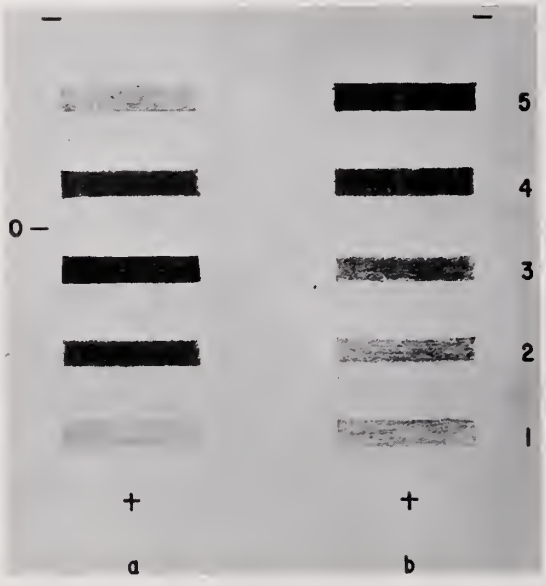


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TABLE I: LDH ISOENZYMES IN NORMAL AND MALIGNANT TISSUES

Organ	No.	Tissues*	Isoenzymes - Percent				
			(-) 5	4	3	2	(+) 1
Stomach	3	N	13	25	28	26	8
		CA	35	34	25	5	1
Colon	3	N	14	22	38	24	2
		CA	39	29	20	11	1
Lung	3	N	16	19	39	21	5
		CA	22	29	44	4	1

** N = Normal; CA = Carcinoma*

TABLE II: MDH ISOENZYMES IN NORMAL AND MALIGNANT TISSUES

Organ	No.	Tissues*	Isoenzyme - Percent	
			MDH_2 (-)	MDH_1 (+)
Stomach	3	N	28	72
		CA	26	74
Colon	3	N	37	63
		CA	35	65
Lung	3	N	45	55
		CA	39	61

** N = Normal; CA = Carcinoma*

monstrable in many instances even before gross or mieroseopie alterations are evident. This would be of greater importance in doubtful, controversial eases or in the eases in which the malignancy is found early in the course of the disease at a time when morphologieal ehanges are not so evident. At this early stage, when recognition of a malignancy is so important from a therapeutie standpoint, the LDH isoenzyme pattern beeomes one of the earliest indications of a later histologieal recognizable malignant growth.

The isoenzymes of malic dehydrogenase are found in the cytoplasm and in the mitoehondria of cells. Both fractions were found in the tissues examined. A deerease in the number and damage to the structure of mitoehondrias has been reported to oeeur in ehemieally induced liver tumors in experimental animals (10). A change of this type would conceivably be refleeted in a decreased conentration of the mitoehondrial (MDH_2) isoenzyme and a relative inerease in the eytoplasmie (MDH_1) isoenzyme. In the malignant tissues analyzed the relative concentrations of MDH_1 and MDH_2 show almost no difference from those of normal tissue. Thus the malie dehydrogenase isoenzyme pattern would be of little value in aseertaining malignant ehanges.

Summary

Electrophoretic isoenzyme determinations provide a new tool for the visualization of enzymatie activity in pathologieal proeesses. Data have been presented which indieate that the lactic dehydrogenase of malignant tissue evidences an inerease in the relative eoncentration of cathodal isoenzymes. The malic dehydrogenase of normal and malignant tissues does not show any differences. We feel that the determination of the laetic dehydrogenase tissue isoenzyme patterns may be an important adjunet in the evaluation of malignant pathologieal ehanges.

Resumen

El análisis por eleetroforésis de los isoenzimas nos ofreee una nueva téenica para la mejor valoración de la aetividad enzimátiea en tejidos normales y patológieos. Utilizando esta téeniea, se ha obtenido una mayor actividad relativa de los isoenzimas eatódicos de la deshidrasa láetiea en tejidos malignos al ser eomparados con la aetividad en tejidos similares normales. Por el eontrario, no se han observado alteraeiones en la actividad de los isoenzimas de la deshidrasa málica en tejidos normales y malignos. Creemos que el perfil isoenzimático de la deshidrasa láetica en tejidos puede representar una valiosa ayuda en el diagnóstico preeoz de procesos malignos.

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URIC ACID LEVELS IN A POPULATION WITH RHEUMATIC COMPLAINTS

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The possible effect of geographical, social, racial, economic and dietary factors in the serum uric acid levels of a population has been a point of study and discussion (1, 2, 3, 4, 5). There have been reports of higher serum uric acid levels in specific ethnic groups when compared to accepted normal values (6, 7, 8, 9); at least three reports have been concerned with people born in the tropical zone (7, 8, 9).

In Puerto Rico, a tropical area, statistically significant studies to determine mean and normal serum uric acid levels in our population are lacking. The only report available is one of a random group of 100 male patients from the Veterans Administration Hospital (10). The values by which hyperuricemia is established are based on mean values done in the United States (11, 12). This scarcity of available data for our country prompted us to study the serum uric acid levels in a representative sample of our population. The first part of this study was done in a group of people with rheumatic complaints, which is the subject of the present paper. The second part of our study, now in progress, is being done in a control group with no rheumatic complaints whatsoever.

Material and Methods

The study was done at the Municipality of Guaynabo, Puerto Rico where 8,652 unselected individuals, 15 years of age and over, were screened by means of a prepared questionnaire, designed to detect potential rheumatic individuals (13). The subjects included in the study came from rural as well as urban areas. The individuals who could possibly or even remotely have a rheumatic condition, suspected by a positive answer to one of the items of the questionnaire, were examined at the Arthritis Research Project Clinic.

A complete history and physical examination was done on each subject. In all of them a hematocrit, sedimentation rate, latex fixation test and serum uric acid determination were done. Radiographic studies were also done including views of the cervical spine, hands, feet, and any other involved joint. The serum uric acid determination was done by the method described by Kern and Stronsky as modified by Archibald (14). This method is based in the ability of uric acid to reduce the tungstate radical of phosphotungstic acid to a lower valence with the formation of a blue color. Blood samples were taken on a fasting state and serum samples were frozen to $-4\ ^{\circ}C$ within three hours after the blood was drawn. The determination of serum uric acid was done during the same week. In each batch of samples a known standard of Chemtrol* was run as control.

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This work was supported in part by PHS grant CD-0003-07. Presented in part at the Annual Meeting of the Alumni Association of the University of Puerto Rico, School of Medicine, September 1967.

**Chemtrol - trademark of Clinton Laboratories, pooled bovine serum used as an internal standard control.*

The first 1,000 consecutive subjects seen at the clinic were included in the present study. The presence of gouty arthritis was evaluated by the criteria established by the New York Symposium on Population Studies (15).

Results

Of the 1,000 subjects studied 235 were males and 765 were females. All of them had rheumatic complaints. Of the group, 48 percent were found to have no rheumatic disease. Rheumatoid arthritis was found in only 35 subjects (3.5 percent), osteoarthritis was found in 461 cases (46.1 percent), discogenic disease alone was found in 22 cases (2.2 percent) while 186 of the 461 osteoarthritics had also discogenic disease by X-ray. Only two subjects, both males, were found to have gouty arthritis (0.2 percent). There were no subjects with renal insufficiency, psoriatic arthritis, myeloproliferative disorders or any of the conditions known to be associated with secondary hyperuricemia.

For the purpose of this study the subjects were divided in age groups as shown in Table I. Among the males, the number of subjects increased in the older age groups. The women were more evenly distributed by age. For both sexes the greatest number of cases fell in the 35 to 54 years interval.

The values found for serum uric acid were from 1.5 mg/100ml to 8.9 mg/100ml. We grouped the values in classes according to the level of uric acid with 1 mg/100ml as the class interval and the frequency distribution was analyzed by sex (see Table II). The lowest value found in the male group was 2 mg/100ml and the highest 8.9 mg/100ml. In the female group the lowest value was 1.5 mg/100ml and the highest was 7.6 mg/100ml. Only two females had a serum uric acid value above 6.9 mg percent while six males had a serum uric acid value above that level. In the male group 51.0 percent were in the range of 4.0 to 4.9 mg/100ml of serum uric acid and 15.7 percent in the range of 5.0 to 5.9 mg/100ml. Therefore 89.3 percent of the group was in the range of 3.0 to 5.9 mg/100ml of serum uric acid. Only 8.1 percent of the males had a value of 6.0 mg/100ml or over, which is considered the

TABLE I: SEX-AGE DISTRIBUTION

Age (Years)	Males		Females		Totals	
	No.	*Percent*	*No.*	*Percent*	*No.*	*Percent*
15-24	20	8.5	86	11.2	106	10.6
25-34	19	8.1	126	16.5	145	14.5
35-44	52	22.1	166	21.7	218	21.8
45-54	48	20.4	174	22.7	222	22.2
55-64	41	17.4	107	14.0	148	14.8
65 and over	55	23.4	106	13.9	161	16.1
Totals	235	100	765	100	1000	100

TABLE II: FREQUENCY DISTRIBUTION OF URIC ACID VALUES BY SEX

Serum Uric Acid (mg/100ml)	Males		Females	
	No.	*Percent*	*No.*	*Percent*
1.0-1.9	0	0	3	0.4
2.0-2.9	6	2.6	140	18.3
3.0-3.9	53	22.6	380	49.6
4.0-4.9	120	51.0	180	23.6
5.0-5.9	37	15.7	52	6.8
6.0-6.9	13	5.5	8	1.0
7.0-7.9	3	1.3	2	0.2
8.0-8.9	3	1.3	0	0
9.0-or over	0	0	0	0
Totals	235	100	765	100

upper limit of normal for serum uric acid values by some authors (11). Using 6.5 mg/100ml as a cutting point only 2.5 percent of the males had a value above this level. The mean serum uric acid for the males was found to be 4.4 mg/100ml with a standard deviation of ± 1.01 mg/100ml.

In the female group 18.5 percent were in the range of 2.0 to 2.9 mg/100ml of serum uric acid. The largest portion of the female group, 49.7 percent, fall in the 3.0 to 3.9 mg/100ml range, while 23.6 percent were in the range of 4.0 to 4.9 mg/100ml. Therefore 91.5 percent of the females had a serum uric acid value in the range of 2.0 to 4.9 mg/100ml. Only 8 percent of the females in the group had a serum uric acid higher than 5 mg/100ml. If we take 5.5 mg/100ml as a cutting point only 3.6 percent of the females had a value over it. The mean serum uric acid value for the females was found to be 3.7 mg/100ml with a standard deviation of ± 0.89 mg/100ml.

The mean serum uric acid value for the whole group was 4.05 mg/100ml. The difference of 0.7 mg/100ml between the mean values for each sex was determined to be statistically significant up to a 95 percent of significance.

The distribution of serum uric acid values as related to sex is plotted in figure 1. It

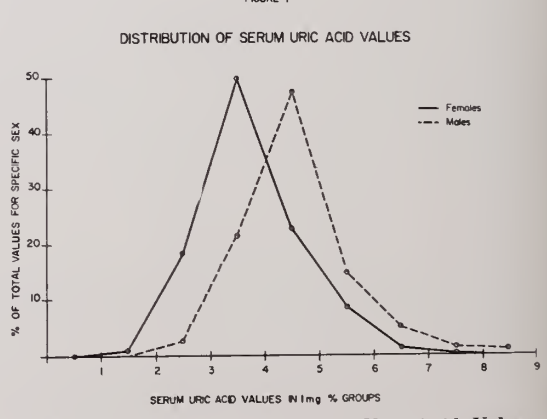


Fig. 1: Distribution of Serum Uric Acid Values

TABLE III: MEAN URIC ACID VALUES

Age (Years)	Females *(mg/100ml)*	Males *(mg/100ml)*	Difference *(mg/100ml)*
15-24	3.2	4.2	1.0
25-34	3.7	4.8	1.1
35-44	3.6	4.4	0.8
45-54	3.7	4.2	0.5
55-64	3.8	4.4	0.6
65 and over	4.0	4.6	0.6
Means	3.7	4.4	0.7

will be noted that the curves although similar in appearance differ for each sex. The curve for the female subjects peaks sharply and higher at a value below the peak of the curve in the male subjects. The peak for the females is at the range of 3.0 to 4.0 mg/100ml of serum uric acid with 49.9 percent of the group at this range. This corresponds to the mean value for females which is 3.7 mg/100ml. The peak for the males is at the range of 4.0 to 5.0 mg/100ml values with 47.4 percent of the males in this range which corresponds to the mean value found for males which is 4.4 mg/100ml.

The relation of mean serum uric values to age and sex is illustrated in figure 2. In the females of group age 15 to 24 the mean serum uric acid is 3.2 mg/100ml while in those of 65 years or over it is 4.0 mg/100ml. In the male group the highest mean serum uric acid (4.8 mg/100ml) is present in the 25 to 34 years age group. In the females the highest mean serum uric acid value (4.0 mg/100ml) was obtained in the group of 65 years and over. The mean serum uric acid values by sex at each age group is stated in Table III. The arithmetic difference between the mean values for each sex, at each age group is given. The difference between males of age 15 to 45 years and the prémenopausal females is .86 mg/100ml while after age 45 the difference between sexes is 0.60 mg/100ml.

Discussion

Serum uric acid may be determined by different methods. The normal value will depend

FIGURE 2

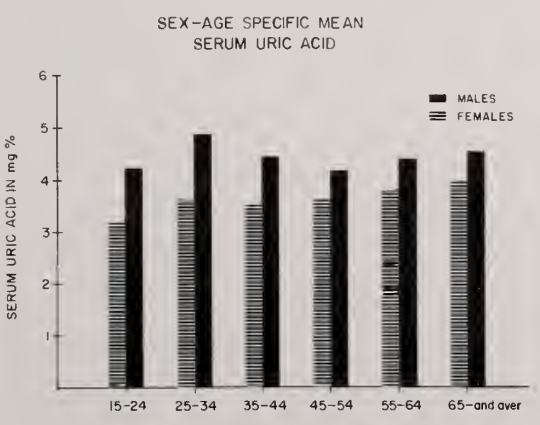


Fig. 2: Sex-Age Specific Mean Serum Uric Acid

on the method selected. Throughout the years many methods have been employed in this determination. The variety of methods have been a barrier in the establishment of uniform levels for hyperuricemia. It has been accepted that the enzymatic method of Praetorious and its further modifications are of complete confidence for serum uric determinations (16). Its drawback is that it requires the use of an ultraviolet spectrophotometer which is not always available in the clinical laboratory. Consequently it is more practical to use a colorimetric procedure which approximates the specific enzymatic one; such as the Archibald modification (14) of the method designed by Kern and Stronsky. The specificity of this method, its quantitative recovery and the reproducibility of its results, which is what is demanded for acceptance of an analytic procedure, were demonstrated in the work of Alper (16). In view of these considerations this method was the one employed by us in this study.

In our study which was done from a group of subjects with rheumatic complaints we found that sex affects significantly the values of serum uric acid. Serum uric acid levels were found higher in males. This has been found in other population studies (17, 18). Before the age of 15 there is no difference in the serum uric acid level between the sexes. This finding was evident in the Tecumseh Study (17) where people of both sexes, four years of age and over were studied. Since our study did not include subjects younger than 15, we could not ascertain this finding. We found that after puberty the mean serum uric acid level is less in females that in males. This finding was also observed in the Tecumseh (17) and England (1) studies. In our study it was found that males at any given age group had a serum uric acid level higher than females in the same group (Figure 2). Before the 45-55 age group this difference is around 1 mg/100ml while after age 45 the females tend to have higher levels, and the difference in the mean for each sex average 0.5 mg/100ml. The difference between the mean value for all males and females was 0.7 mg/100ml which is the same difference reported in the Tecumseh study (17), although their mean values were different to ours. In our study the distribution of values along life varies little for the males, who only show a slight rise at age 25-34 and some increase after age 65. The females show a gradual increase in uric acid levels with increase in age being this more prominent after the 45 years. At this age group the mean values for each sex show a difference of 0.5 mg/100ml which was the same found in the England study (1), where the age-group distribution was similar to ours. These higher levels in the women after age 45 have been attributed to the menopause; it has been explained on the basis of a greater renal clearance of uric acid in the premenopausal female (12).

The normal values for our group of subjects with rheumatic complaints were determined by the accepted formula that: a mean value plus or minus two standard deviations is equal to the normal limits. The mean value of serum uric acid for males was 4.4 mg/100ml. The addition of two standard deviation (SD_{Males}= 1.01) gave an upper normal limit of 6.5 mg/100ml. Only 2.5 percent of the males had values above this level. In the female group the mean value was 3.7 mg/100ml and the addition of two standard deviation ($SD_{Females}$= 0.89) gave an upper limit of normal of 5.5 mg/100ml. Only 3.6 percent of the females had values above this level. This slightly larger percent is only a reflexion of the fact that a greater frequency of higher values for uric acid are found in the postmenopausal female causing skewing of its distribution curve.

The determination of upper limits of normal for uric acid has been done arbitrarily

most of the time, even in large excellent studies, such as the one done on Framingham (18). The availability of a large number of individuals of different sex and age groups as in our study, gave us the opportunity to analyze the distribution of values by mathematical means. Upper limits of normal can be determined by the use of the properties of the "normal curve" and by this way hyperuricemia can be defined. This was recommended in the latest Symposium of Population Studies (15) as the only way to establish limits for hyperuricemia for each population under study. By this way we establish hyperuricemia in our population as any value of uric acid above 6.5 mg/100ml in males and 5.5 mg/100ml in females, using a colorimetric method for its determination.

Of the rheumatologic conditions the only ones associated with hyperuricemia are gout and psoriatic arthritis. In our group 48 percent of the subjects had no rheumatic disease. Only two had gout and none psoriatic arthritis. This permits us to postulate that probably our upper limits of normal values will be good guidelines for hyperuricemia in Puerto Rico, as similar distribution curves have been found in unselected population studies (17).

Summary

Serum uric acid determinations were done in 1,000 subjects from the Guaynabo Community. All of them were seen at the Arthritis Research Project because of rheumatic complaints. The urie acid values obtained ranged from 1.5 mg/100ml to 8.9 mg/100ml. The mean value for the whole group was 4.05 mg/100ml, being for the males 4.4 mg/100ml and for the females 3.7 mg/100ml. The upper limits of normal for the group established by a normal distribution curve gave a value of 6.5 mg/100ml for males and 5.5 mg/100ml for women in our group of subjects with rheumatic complaints.

Resumen

El nivel de ácido úrico en el suero de 1,000 personas del pueblo de Guaynabo fue determinado. Todas estas personas fueron examinadas en el Proyecto de Investigaciones de Artritis, debido a quejas reumáticas. Los valores de ácido úrico obtenidos estaban entre los límites de 1.5 mg/100ml a 8.9 mg/100ml. El valor medio para el grupo fue de 4.05 mg/100ml. Los límites superiores de lo normal de ácido úrico, establecidos para nuestro grupo usando una curva de distribución normal, fueron 6.5 mg/100ml para los varones y 5.5 mg/100ml para las mujeres.

Acknowledgment

We are grateful to Raquel Torres, BS, MS for her assistance in the statistical analysis of our data and to Ruth Quiñones, BS, MT for the laboratory determinations of serum uric acid.

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CASE REPORT

BICLONAL GAMMOPATHY IN A PATIENT WITH A LYMPHOPROLIFERATIVE DISEASE

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The presence of dysproteinemia with an "M" component in the serum has been associated with several disease processes. The most common causes of the "M" spike is multiple myeloma, but it has also been described in Waldenstrom's macroglobulinemia, heavy chain disease, other forms of lymphoma, and in elderly patients with no evidence of disease (1). This latter entity has been named essential or benign monoclonal gammopathy (2). In rare occasions an "M" spike has been present in association with thymomas (3), chronic granulocytic leukemia (4), polycythemia vera (5), acute leukemias (6), carcinoma of the breast, carcinoma of the prostate, carcinoma of the gastrointestinal tract and even Gaucher's disease (1).

The "M" component can be identified as belonging to one of the five main classes of immunoglobulins, Ig G, Ig A, Ig M, Ig D or Ig E (7). The immunoglobulins are composed of heavy chains and light chains. The heavy chains of the five immunoglobulins are antigenically distinct and this permits their identification by immuno-assays. The light chains are of two types, kappa (Type I) and lambda (Type II) and are common units to the five classes of immunoglobulins. Bence Jones proteins are light chains. The presence of two immunologically distinct "M" components in serum or two types of Bence Jones proteins in the urine has been rarely described in multiple myeloma (8, 9, 10). In lymphosarcoma and chronic lymphatic leukemia a single "M" component is found occasionally (11) but the occurrence of 2 "M" spikes is most unusual.

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This study was supported by Hematology Training Grant No. T1 AM 5302-05.

Presented at the Scientific Meeting of the 7th Annual Convention of the Alumni of the University of Puerto Rico School of Medicine, September 1, 1967.

Case Report

A 74-year-old woman was found to have splenomegaly in 1964. She had several blood studies done including a bone marrow, which revealed an increased number of mature lymphocytes. She did not receive treatment until 1966 when she began having frequent colds, skin pustules, ecchymosis and nose bleedings.

On physical examination she was found to have a large spleen, but no adenopathy. The skin showed many purpuric lesions mostly over the forearms. The hemoglobin was 10g per 100 ml, the WBC 4,450/cu. mm with 51 lymphocytes, 45 segmented polymorphonuclears, one stab and three monocytes. The reticulocyte count was 1.7 percent. The bone marrow revealed an infiltration with mature lymphocytes and some prolymphocytes (Figure 1). The urinalysis, fasting blood glucose, blood urea nitrogen and the serum uric acid were normal. The total serum protein was 8.2 g per 100 ml with 2.9 g albumin and 5.3 g globulin. The serum protein filter paper electrophoresis revealed two "M" components in the region of the gamma globulin. The patient was referred to her local physician with a diagnosis of lymphocytic lympho-

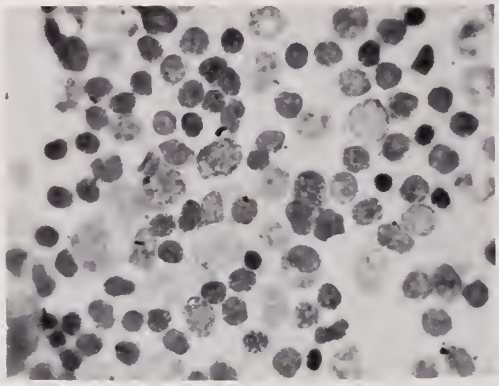


Fig. 1: Bone marrow showing infiltration with mature lymphocytes and prolymphocytes. Wrights Giemsa x 500.

sarcoma involving the bone marrow and therefore in a leukemic phase.

In January 1967 she was seen because of repeated bouts of bronchitis and weight loss of 20 pounds. The spleen was large and extended 14 cm below the costal margin. The liver was felt 1 cm. below the right costal border. The hemoglobin was 9 g per 100 ml, the WBC 3,000/cu.mm and the platelet count 90,000/cu.mm. The bone marrow was unchanged. The PPD had 15 mm of induration and the histoplasmin skin test was 7 mm in diameter. The stools were negative for occult blood, ova and parasites. Treatment with prednisone 40 mg. orally daily was instituted and after one month there had been a considerable decrease in both "M" spikes. Cyclophosphamide (Cytoxan ®) was started in a dose of 50 mg orally daily and the predisone was slowly decreased to 15 mg daily.

A repeat bone marrow six months after initiating therapy was normal and the spleen decreased in size to 1 cm below the right costal margin.

Special Studies

The serum paper pherogram revealed 37.7 percent albumin, 3.0 percent alpha 1, 6.2 percent alpha 2, 7.9 percent beta and 45.2 percent gamma globulin. Two distinct "M" components were present in the region of the gamma globulin (Figure 2).

Serum protein immunoelectrophoresis using the method described by Grabar (12) revealed the pre-

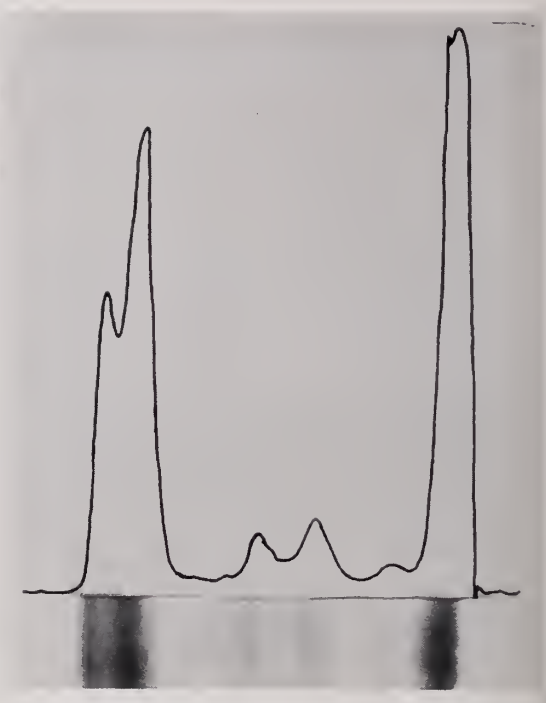


Fig. 2: Serum paper electrophoresis showing the two distinct "M" spikes.

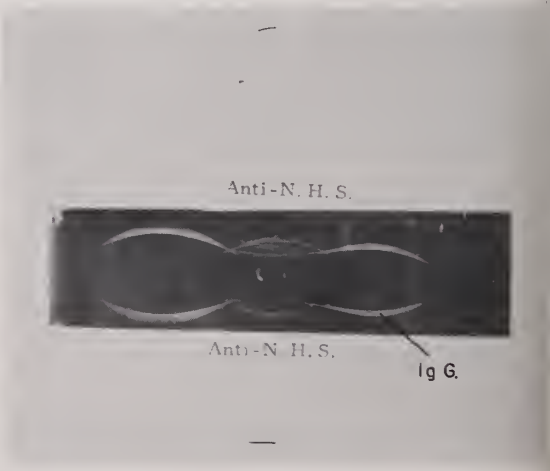


Fig. 3: Serum immunoelectrophoresis showing the large IgG band.

sence of a broad arc in the region of IgG (Figure 3). This was confirmed by using specific anti IgG, anti IgA and anti IgM antisera obtained commercially*. Only with the anti IgG serum was a precipitin band observed (Figure 4). The radial immunodiffusion assay* was used to measure the serum immunoglobulin concentration. The serum IgG was 6,000 mg/100 ml (normal 600-1200 mg/100 ml), IgA was 58 mg/100 ml (normal 70-200 mg/100 ml) and IgM was 75 mg/100 ml (normal 40-100 mg/100 ml).

With immunoelectrophoretic techniques using specific anti-light chain sera*, anti kappa and anti lambda, we were able to detect a large band against kappa and a smaller band against lambda light chains (figure 5). This confirmed the presence of two distinct antigenic proteins in the serum.

Immunofluorescent study of the bone marrow was done using fluorescein conjugated anti IgG, anti IgA and anti IgM* (13). The quality of the conjugated product was confirmed by immunoelectrophoresis. Fluorescein conjugated anti-light chain sera was not available when we studied this patient. The bone marrow smears and peripheral blood buffy coats were fixed in 95 percent ethanol for 1 minute and washed in phosphate buffered saline (PBS) at pH 7.4. Smears were incubated individually with fluorescein conjugated goat anti-human IgG, anti IgA and anti IgM for 30 minutes. They were washed with PBS three times for five minutes each time. The smears were mounted in 0.025 PBS at pH 7.4 and a cover glass. The smears were studied within 24 hours. For control we used smears pretreated with unconjugated goat antihuman IgG, anti IgA and anti IgM in order to block the reaction. After 30 minutes of incubation with antisera at 37°C the smears were washed three times with PBS and then were processed with unconjugated antisera as described above.

We were able to demonstrate fluorescence in the cytoplasm of about 15 percent of the bone marrow lymphocytes using fluorescein conjugated anti IgG and not with the others. Plasma cells which had cytoplasmic fluorescence with anti IgG and anti IgA were also detected although they were scarce. The fluorescence was considerably reduced in the smears pretreated with unconjugated antisera. No fluorescence was observed in the peripheral blood lymphocytes.

**. Obtained from Hyland Laboratories, Los Angeles, California.*

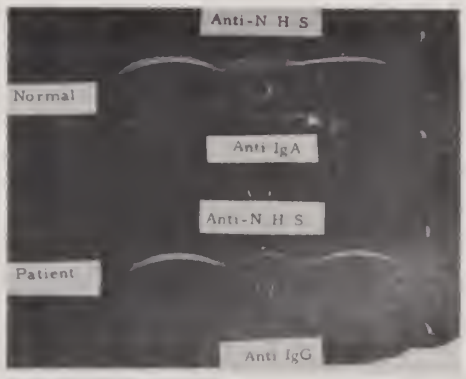


Fig. 4: Serum immunoelectrophoresis using specific anti sera showing the single IgG band in the patient. A normal control is shown above.

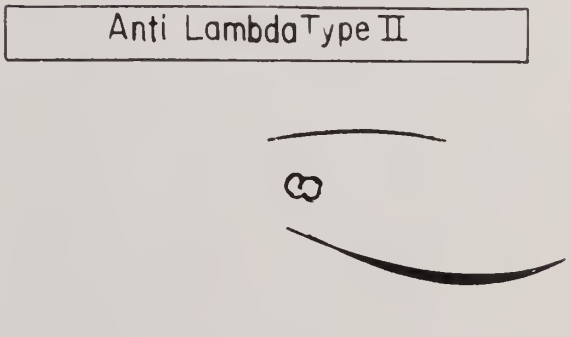


Fig. 5: A combined picture and schematic representation of the immunoelectrophoresis using specific anti kappa and anti lambda sera shows the precipitin bands.

Discussion

This patient has a lymphoproliferative disease which can be diagnosed as chronic lymphatic leukemia although it resembles more a lymphosarcoma of the spleen with bone marrow infiltration. The immunologic studies

revealed that her disease is associated with the production of two antigenically distinct "M" components. We were able to demonstrate that besides the plasma cells, the lymphocytes in the bone marrow of this patient could synthetize IgG. Similar results have been reported by Gamble (14) who studied a patient with chronic lymphocytic leukemia who had an IgG "M" component. He was able to demonstrate the presence of IgG in the cytoplasm of lymphocytes in the bone marrow, lymph nodes and peripheral blood. He concluded that a small number of lymphocytes may also contribute to the formation of immunoglobulins under normal circumstances.

In multiple myeloma the occurrence of an abnormal "M" component and Bence Jones protein is a frequent occurrence. It is not known if both proteins are synthetized by the same plasma cells. Two different Bence Jones proteins have been described in multiple myeloma (9). The simultaneous occurrence of IgG and IgM paraproteins has also been described (15). In 1965 Voerman *et al* (16), reported a patient with myeloma who had two "M" components of different sedimentation constants, 7S and 17S, however, both proved to be IgA, the 17S component being a polymerization of IgA molecules. Two serum "M" components have since been detected in about 25 patients with multiple myeloma (10). Bachmann (17) studied 585 sera with "M" components and found seven with two "M" peaks. Four had multiple myeloma, two had carcinoma and one had reticulum cell sarcoma and a renal carcinoma. The occurrence of two "M" components in a patient with polycythemia vera has been reported (5).

It has been proposed that if the presence in multiple myeloma of one "M" spike means one clone of neoplastic cells; the presence of two distinct paraproteins is evidence of two different neoplastic clones of cells. In a recent study Costea *et al* (18) reported a patient with two myeloma globulins, IgG and IgA. They demonstrated by immunofluorescent techniques that these immunoglobulins were simultaneously present in individual plasma cells. His evidence suggests in that patient that one clone of plasma cells can produce more than one type of immunoglobulin. In a more recent study Rosen *et al* (12) presented evidence that the two serum "M" components in a patient with multiple myeloma were originated in two different cell populations.

In our patient although the lymphocytes had IgG in the cytoplasm, since plasma cells were present which also had IgG, we cannot state whether the lymphocytes were producing both paraproteins or if the plasma cells were contributing one of the "M" components. We feel that the scarce number of plasma cells present and the prompt suppression of both spikes after one month on prednisone suggest that the lymphocytes were synthetizing both paraproteins.

Summary

A 74-year old patient with a lymphoproliferative disease was found to have two "M" components in the serum. Immunoelectrophoretic studies showed that both components were IgG but they had different light chains. The largest component was kappa (Type I) and the smaller was lambda (Type II). Immunofluorescent studies of the bone marrow showed that lymphocytes had IgG in their cytoplasm confirming our impression that these cells were producing at least one of the serum "M" components. Therapy with prednisone produced clinical improvement and prompt suppression of both spikes.

Resumen

Una paciente de 74 años que padece de

un desorden linfoproliferativo tenía dos componentes "M" (paraproteínas) en el suero. Estudios de inmunoelectroforesis demostraron que ambos componentes eran de inmunoglobulina G (IgG), pero que tenían distintas cadenas livianas. El componente mayor era de cadenas kappa (Tipo I) y el componente menor era de cadenas lambda (Tipo II). Estudios de inmunofluorescencia en la médula ósea demostraron que los linfocitos tenían IgG en el citoplasma, confirmando nuestra impresión que estas células estaban produciendo por lo menos uno de los dos componentes "M". La terapia con prednisona mejoró a la paciente y suprimió ambos componentes "M".

Addendum

Since the preparation of this manuscript a patient with lymphosarcoma with Bence Jones proteinuria type K and serum IgG type L has been described (19). The description of similar cases will undoubtedly continue.

Acknowledgment

The authors are grateful to Miss Norma Sánchez and Miss Jane Roseborough for their technical assistance. We also want to thank Dr. Roberto López-Busquets who referred this patient to us.

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GRAND ROUNDS, UNIVERSITY HOSPITAL

Lupoid Hepatitis

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Lillian Haddock, MD

Dr. Ginés Martínez:*

A 21-year old mulatto female was admitted to the University Hospital on January 27, 1967 with jaundice. The history of the present illness dated back to four years prior to admission when the patient developed pain, swelling and stiffness of the ankle, elbow, knees and wrist joints. During these four years she had intermittent swelling, pain and redness of these joints, which at times was so severe that it incapacitated her to do any type of work. Otherwise, she was fairly well until two and a half months prior to admission when right after having her luncheon meal, she developed a mild to moderate epigastric pain accompanied by nausea and vomiting. She was seen by a private physician who prescribed several medications. She improved and continued feeling fairly well until one week later when she noticed that the sclerae of her eyes were yellow. Infectious hepatitis was diagnosed and she was placed on strict bed rest. She noticed acholic stools and dark yellow urine but denied having had any fever, generalized malaise, anorexia, right upper abdominal quadrant pain, diarrhea nor constipation. There was no history of contact with icteric persons, blood transfusion nor ingestion of any particular drugs. Laboratory tests performed while being seen by her private physician gave the following results: SGPT, 106-268 units; total bilirubin from 14.5 to 28 mg/100 ml; alkaline phosphatase, 8-11 King-Armstrong units and a Hanger's test of 4+ at 24 hours. She was treated with intravenous fluids, a low fat high carbohydrate diet and multivitamins. A gall bladder series revealed no visualization of the gall bladder. Two weeks prior to admission she developed generalized pruritus and some discrete vesicular lesions in the skin. One week prior to admission she had epistaxis and two weeks before she noticed bright red blood in the stools. She was then referred to our hospital for further evaluation and treatment. She denied any history of photosensitivity, alopecia, dysphagia or other skin changes.

The family and past medical history were non-contributory.

Physical examination revealed a well developed well nourished female who was jaundiced but in no acute distress. The eyelids were edematous and the sclerae were icteric. There were two small blood clots, one in each nostril. The tonsils were hypertrophied. In the neck there was a 2 cm rubbery, non tender, fixed node in the left posterior cervical triangle and a 1.5 cm rubbery movable node in the right side of the neck. The examination of the heart and lungs was essentially normal. The abdomen was distended; the liver was palpable 3 cm below the right costal margin and it measured 14 cm on percussion; the spleen and kidneys were not felt. The skin

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was icteric and multiple small crusted vesicles were present in the chest, abdomen, back, arms and legs. The rest of the physical findings were normal.

Laboratory studies revealed: hematocrit, 32 percent; urine analysis was negative for albumin, sugar and cells. BUN was 8 mg/100 ml, serum creatinine, 0.8 mg/100 ml, alkaline phosphatase 18 K. A. units, SGOT 520 units, SGPT 150 units, total bilirubin 27.2 mg/100 ml, direct bilirubin 10.8 mg/100 ml, serum sodium 130 mEq/L, serum potassium 3.7 mEq/L, serum chloride 110 m/Eq/L, CO_2 combining power 23.4 mEq/L, platelet count 52,500/cu.mm, prothrombin time 36 secs with control of 15 seconds, VDRL non reactive, bleeding time 6 1/2 minutes, clotting time 8 1/2 minutes Direct Coombs test was positive on two occasions. The LE cell preparation was positive, antinuclear antibodies were present and classified as 2+ diffuse. A sickle cell preparation was positive. The reticulocyte count was 5.5 percent. The total serum protein was 7.1 gm/100 ml, albumin 2.0 gm/100 ml, and globulin 5.1 gm/100 ml; the serum protein electrophoresis showed 18.4 percent albumin, $alpha_1$ globulin 2.9 percent, $alpha_2$ globulin 1.6 percent, beta globulin 5.7 percent and gamma globulin 73 percent. The latex fixation test was positive 1:640.

Radiological studies revealed non specific coarsening of the mucosa of the stomach and duodenum, findings in the esophagus suggestive of those seen in sclcroderma and no evidence of esophageal varices. The chest plate and bone survey were normal.

The course in the hospital was complicated. One day after the admission she developed epistaxis and hematochezia. She was given 50 mg of Aqua Mephyton® intravenously and the epistaxis stopped. Three days after admission she had gained 5 pounds. She was placed on a low salt diet. On February 2nd she was started on 60 mg of prednisone daily. On February 6th she was uncooperative and restless. A fasting blood sugar was 40 mg/100 ml and she was given hypertonic glucose intravenously. On the next day she was found semicomatose restless and unresponsive. The liver on this day measured 8 cm on percussion. She was given hydrocortisone intravenously, Modumate® 100 g daily, neomycin 8 g daily and 10 percent dextrose in water. The next day she was markedly improved and her sensorium was clear. Two days later she developed, nausea, vomiting and flapping tremors. She was started on prednisolone 60 mg intramuscularly daily and enemas of neomycin were given. On February 11th she was again much improved well oriented and cooperative.

Clinical Discussion

Dr. A. McGehee Harvey:*

Most of the evidence in this patient favors a hepatic type of jaundice. She had a rather high total bilirubin level, the transaminase values were considerably elevated, the alkaline phosphatase was not significantly elevated and the flocculation tests were altered. All of these findings together with a prolonged prothrombin time which did not return to normal after parenteral vitamin K indicates diffuse impairment of the hepatic function. There was no obvious predisposing cause or any exposure to suggest she had a viral or serum hepatitis. She had not been taking any drugs. This all appeared "out of the blues", and certainly was compatible as far as the laboratory findings are concerned with a viral type of hepatitis. However there were certain features that cannot be adequately explained if she

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had a viral hepatitis. First of all she has been ill for a much longer period of time. In the average patient with viral hepatitis the jaundice reaches a peak in about 10 days, then levels off and begins to decrease. Furthermore this patient had a very large amount of indirect reacting bilirubin, which coupled with a decreasing hematocrit and an elevated reticulocyte count suggests that some type of hemolytic process was going on. Many patients with liver disease show a hemolytic type of anemia of variable degree, but seldom in the ordinary case of viral hepatitis do we see this degree of hemolysis going on. In addition to the fact that the course of this patient's hepatitis is more severe than one ordinarily expects to see there are some other unusual features. One of these features is the high globulin level this patient has. There are types of liver disease in which the globulin may be elevated but a total globulin of 5 g per 100 ml is certainly not seen in the vast majority of the patients with ordinary viral hepatitis. When you see a globulin of 5 g per 100 ml, it brings to your mind a very limited number of types of illness that can be associated with such a hyperglobulinemia. Such diseases include plasma cell disease, certain of the collagen or autoimmune diseases most characteristically lupus erythematous, sarcoidosis, lymphopathia venereum, certain infections such as chronic active tuberculosis and disseminated neoplastic disease. A few years ago we went back and looked at all of the patients who had their globulin level examined in our laboratories and when the globulin level was 5 g per 100 ml or over, well over 90 percent of the patients fell into one of those diagnostic categories that I just outlined. The fact that she has a hyperglobulinemia of this degree immediately narrows the diagnostic possibilities considerably. In other geographic areas, parasitic diseases such as kala azar are very characteristically associated with tremendous hyperglobulinemia.

I think that this lady can be probably labelled as having what is known as chronic active hepatitis. She has a hepatitis that has continued being active to a degree that she has developed all of the clinical manifestations of hepatic insufficiency. In the average case of chronic active hepatitis, which is a very difficult clinical syndrome to define, one sees a histological stage of postnecrotic cirrhosis and characterized by large scars in the liver with considerable infiltration of lymphocytes and plasma cells.

This syndrome of so called chronic active hepatitis very characteristically occurs in females in the childbearing age period, and this of course is of interest because this is the same setting in which one sees various of the so called autoimmune diseases. This clinical syndrome was first described by Kunkel and his group (1) who thought this was some peculiar type of biliary cirrhosis that occurred in young females and was characterized by a very high serum globulin. Others, who had seen these patients began to notice that many of these ladies with chronic active hepatitis had clinical manifestations characteristic of the syndrome of systemic lupus erythematosus. These varied from very mild clinical manifestations including history of joint pains and swelling not leading to destructive changes in the joints, skin lesions characteristic of lupus, occasional renal involvement and not infrequently hematological findings as one sees in lupus such as leucopenia and thrombocytopenia. A significant number of these patients were shown to have positive L E cell tests indicating that these patients have a circulating antinuclear antibody in their serum. When these findings were first pointed out there was much speculation as to what this meant. It was thought at first that in the presence of severe hepatic cell damage the proteins in the liver may get altered, so that the body looks at them as

foreign proteins and reacts by manufacturing antibodies against these altered proteins. But as more of these cases accumulated it became pretty evident that not only did these patients developed such symptoms in the midst of their chronic active hepatitis, but as you looked very carefully many of them had manifestations quite characteristic of lupus for a number of years prior to the development of the hepatitis, just as this patient had. These patients who develop these protein abnormalities either before, during or after the hepatitis has subsided may later develop both clinical and laboratory evidence of systemic lupus erythematus. So that creates the setting in which one has to try and decide what the syndrome of chronic active hepatitis really means and what is its relationship to autoimmune disease and systemic lupus erythematosus.

When we look at these patients abnormalities we see that she had this unusual type of hepatitis with a very high serum globulin, she is a female in the childbearing age and has a rather striking thromboeytopenia which seems out of proportion to what you would see in hypersplenism. She has in addition evidence suggesting an active hemolytic anemia which certainly is not usually seen in the average case of hepatitis. She has hypergammaglobulinemia, an elevated latex fixation test which is of course not uncommon in any type of liver disease, positive antinuclear antibodies, and recurrent joint pains of which there is nothing specific but which on the other hand are quite compatible with the type of joint difficulties that one sees in patients with lupus erythematosus.

The average case of lupus may be a very mild affair and may go on for many years without really serious episodes of illness. So in that setting lets address ourselves for a moment to what is chronic active hepatitis?, what does it mean?, what is its relationship to lupus erythematosus? In the process of trying to address oneself to this question it becomes necessary to give one's opinion as to what lupus erythematosus is.

What I will say, will be largely my own view based on mainly clinical observation over a period of many years. I will try to construct a working hypothesis as to how one can explain all the clinical patterns that one sees in this area of disease. I am not going to attempt to review the whole of the various clinical and laboratory manifestations that one sees in any patient with classic lupus erythematosus, you know that as well as I do.

One has to define the syndrome of lupus erythematosus. Lupus erythematosus is a clinical state in which the patient has an unusual tendency to develop a variety of immunologic phenomena that reflect themselves in a whole vast array of clinical manifestations: fever, joint pains, pleuritis, pericarditis, involvement of various organs most notably the heart and the kidney, hematological changes such as leucopenia, thrombocytopenia, hemolytic anemia and most important an elevation in the serum gamma globulin and what can be classified as autoantibodies. These autoantibodies are characteristically formed against various components of the cell nucleus. The plasma cell is the cell that manufactures antibodies and it may seem paradoxical that the patient with lupus develops antibodies against the nuclear component of these cells. As you are aware antibodies appear in these patients against nucleoproteins, DNA and various other components of the cell nucleus and cytoplasm. As an example, 20 percent of patients with lupus erythematosus will have a false positive test for syphilis.

As you will remember from your bacteriology course, antigens are proteins that because of their structure if they are harmful to a given species will excite an immunoresponse of one or two major types that lead to the production of humoral antibodies, or to the

development of the delayed or cellular type of hypersensitivity response that is exemplified by the tuberculin reaction.

There are certain types of antigens that are known as good; that is when you inject them into a foreign species a very excellent type of antibody response occurs. There are many others which elicit either no antibody response or only a very slight antibody response. So one can, in simple terms divide the antigens into good antigens and poor antigens.

We can look at lupus not as a disease but a syndrome that is characterized by this particular type of difficulty. Now as evidence has accumulated it seems reasonable to hypothesise that we are not dealing with a disease, but we are dealing with a diathesis, that is the patient may have since birth immunological responses of the certain types I have just described. As they go through life and come into relationship with some powerful antigenic stimulus, whether a vital infection as this patient may have had, whether it is some drugs that they have been given or any other possible exciting stimulus, the disease may become manifest.

Now, if you have a diathesis (I know it is a poor term but I can't think of a better one we could use) it can be of various degrees. You know that some people have mild hay fever, some have severe hay fever and some have hay fever in between. I think one can look upon the patient with lupus as having a diathesis where this abnormal immunological responsiveness is present throughout life. For some reason lupus is particularly prominent in females, and more so in the childbearing age period.

One can have a very mild diathesis so that one can go through life and if a proper triggering event of a serious degree did not appear, one might have these vague joint pains once in a while or other symptoms that might never take one to the doctor. This diathesis might never come to the surface unless one gets a very severe illness like a severe viral hepatitis or is given a drug like isoniazid or hydralazine. If one has a diathesis of moderate degree, spontaneous symptoms may appear from time to time. Other patients have a severe diathesis and these are the ones that may get spontaneous acute fulminating lupus erythematosus.

Now, what is the evidence that this may be the case? One can't just pull a hypothesis like that out of the sky? One has to have some kind of reasonable evidence to support it. Well, a number of years ago, right after World War II a very interesting group of patients was accumulated for a totally different purpose. One of the problems at that time that bothered the syphilologist was the problem of the patient with a chronic false positive serologic test for syphilis. They had great difficulty at that time in telling whether a patient who had a positive serologic test for syphilis had syphilis or not. And this of course was a very important decision at least from the social point of view if nothing else, since many a young lady who had a positive serologic test for syphilis was sent by her father out the front door forever for he made the worst assumptions. Actually as it turned out she should have been very happy had it been syphilis rather than a false positive test for syphilis. In 1949 came the treponema inmobilization test which does identify the true antibody to the treponema in contrast to the serologic test which is a non specific type of an antibody response. It became possible to clearly differentiate those patients who had a chronic biologic false positive test.

Now, I am not talking about an acute false positive reaction which you may see as a transitory phenomenom associated with a great many viral infections. A chronic false

positive test is the one that stays elevated for more than 6 months, provided medical examination and specific tests eliminate the possibility of syphilis. When the patients with a false positive test for syphilis were sorted out it was very interesting that they could be superimposed as to age and sex with a series of patients with lupus erythematosus and we knew that patients with lupus had a very high incidence of false positive test for syphilis. Thus, we had in our hands, back in the early 40's about 200 patients with a chronic false positive biological test for syphilis, test which had been ordered as a routine or for one reason or another, none of whom had any significant illness at all. So we undertook to follow these individuals and see what happened, in other words to see if this group represented a group of people with a "autoimmune" diathesis that we had been able to pick up because of this abnormal antibody response. For the past 15 years we have been following this group of patients. In that period of time, fully 10 percent of them have now developed classical lupus erythematosus, a half a dozen have developed classical Hashimoto's disease of the thyroid as well as a number of other clinical manifestations that are entirely compatible with LE. So that one can look upon this group of patients as having a lupus diathesis, the first expression of which was a false positive serologic test for syphilis. It is interesting that in three of these patients who are still well and who have not developed any clinical evidence of lupus, in addition to developing a positive Wasserman test they have developed a positive test for LE.

So I think all this adds to the impression that there may be a lupus diathesis, that some one has this diathesis from birth, and it may be mild, it may be moderate or it may be severe and what happens to their whole life story of illness is affected to an important degree by having this diathesis.

Now lets look at other lupoid syndromes. As I indicated we have the same problem in relation to the administration of a variety of drugs. We know that patients with lupus have an unusual tendency to develop activation of their lupus when they take certain drugs. Now, in addition there have been now reactions to a number of drugs in which the patient looks apparently well except for the illness for which they were given the drugs. Upon administration of these drugs, they suddenly develop all the manifestations of lupus erythematosus. These drugs include hydralazine, hydantoin, INH, procaine amide and others. In the beginning it was thought that this was a peculiar type of toxic reaction to the drug, but as sufficient cases of lupus developed it became evident that the drug most likely precipitated the manifestations of an underlying disease. The first idea about this occurred to us when we saw two patients with a hydralazine reaction who were followed in the clinic and eventually developed the clinical picture of lupus. Going through the record they had had a very high serum globulin and when you questioned them more carefully there had been a history of recurrent arthritis. Thus if the diathesis is very mild it may not give any symptoms until they get the drug, once they get the drug they develop an acute lupus erythematosus. When the drug is stopped, depending again on the degree of the diathesis, all the active evidences of lupus may disappear or some of them may disappear, or it may disappear very very slowly. One case in our false positive test for syphilis series had been asymptomatic until she received penicillin. She got a typical lupus like reaction which subsided and then two years later the LE cells reappeared without any inciting drug or any thing else and without any active clinical illness.

Another area of interest is the case with classical rheumatoid arthritis in 15 to 20 per-

cent of which you may find positive LE cells. These patients, who may have had classical rheumatoid arthritis for 6 or 7 years, may suddenly develop the clinical picture of disseminated lupus erythematosus. Over a period of years, when you get experience you will find that is very hard to separate these two diseases syndromes. In one extreme we have patients with classical rheumatoid arthritis and at the other extreme you have classical LE with only mild joint aches and no joint deformities. One may see all types of combinations of these autoimmune diseases. For example we may see a patient with lupus who also had Hashimoto's disease. You may see a patient with Sjögren's and the majority of these patients with Sjögren's have another autoimmune disease such as rheumatoid arthritis, scleroderma or with an arteritis which is indistinguishable from polyarteritis nodosa or with a picture of polymyositis.

These diseases are cross over or transitional syndromes. These patients have some sort of a basic abnormality of their immune apparatus and they may develop one of a series of diseases whether they get lupus or rheumatoid arthritis or dermatomyositis or a combination of these diseases may depend on what the whole history of their antigenic exposure is or to the severity of this diathesis.

In addition to the classical disease syndromes that we learn about from the textbooks in these areas you see much more frequently patients who obviously have some type of what we call autoimmune or collagen diseases but in turn it is very difficult to assign it clearly to one of these specific diagnostic categories.

Nobody knows, for example, whether all these abnormal antibodies are the cause or the effect and is perfectly possible at the moment that we may be dealing with an infectious disease and we have not yet developed the proper techniques to recognize the infection.

In closing, lets compare the current situation in regard to systemic lupus erythematosus to that which existed in relation to syphilis. For over four centuries there was tremendous debates about all of the various manifestations that are related to syphilis. Syphilis, just like lupus is a chronic disease which shows various periods of activity that go on over a period of many, many years. Before 1903, clinicians had great difficulty in its diagnosis since the period from the development of the chancre to the development of the aneurysm or general paresis was a matter of 15 to 20 years. So trying to determine whether optic neuritis, or deafness or cardiovascular disease or central nervous system disease was due to syphilis was a matter of great debate in those periods. For over four centuries nobody knew that all of this was due to infection with treponema. When the *Treponema pallidum* was discovered in 1903, and then a few months later Wasserman described his blood test all of this controversy disappeared. It was then quite evident that aortic insufficiency, the aortic aneurysm, the general paresis and the chancre were all due to this infectious illness.

It could be that lupus may turn out to be due to an infectious agent. All I am saying is that we really understand this disease area very poorly at the moment, but at least we have learned certain things regarding the management of these patients which has stemed from our interpretation that they are concerned in some way with immunological mechanisms. The use of steroid therapy has been very effective in inhibiting antibody formation and delaying hypersensitivity reaction. The use of immunosupressive agents which act by inhibiting protein synthesis in the cell and antibody formation must be considered as yet experimental.

So, in closing this is a very complicated problem, and I think this patient this morning illustrates one of the more complicating pro-

blems in this over all area of disease. The answers that I have tried to give you this morning are purely speculative based on trying to put together a mass of clinical observations made over a series of many years of seeing patients that have disease in this general area.

Dr. Carlos Rubio:

Of your 200 patients with a false positive serology, has any of them reverted to normal?

Dr. A. McGehee Harvey:

There is a significant number of families in which there are false positive serologies in at least three generations. We have not included in these series anybody who has not had a positive test for over six months. We have not attempted to have it influenced by any drug. Sixty five percent of the subjects are females. Up to date no male in this series has developed a disease that we can call autoimmune. It occurs only in females.

Dr. J. E. López:

This patient also had disturbance of esophageal motility.

Dr. A. McGehee Harvey:

Upper or lower?

Dr. G. Martínez:

In the upper esophagus.

Dr. Heriberto Pagán:

The patient had an atonic, dilated esophagus. There is coarsening of the duodenal mucosa. We did not do a small bowel series.

Dr. A. McGehee Harvey:

We have been doing in all our patients barium swallow and motility studies and it is not unusual to have clear cut changes in the esophagus in patients with lupus without having dysphagia as those seen in scleroderma and dermatomyositis. Thus you can see cross over.

Dr. Carlos Rubio:

Patients with lupoid hepatitis have a viral disease and then have this diathesis; what about lupus patients that get a transfusion and develop a reaction. Is it more severe?

Dr. A. McGehee Harvey:

Only two patients in this group have developed hepatitis. Unfortunately it happened in two males and we cannot say that the hepatitis was worse. A hepatitis in a patient with lupus is more severe and it tends to be prolonged. Again it is very hard to get well controlled evidence. What we are dealing with here is a well defined clinical problem in a young girl who gets hepatitis.

Dr. Francisco Aguiló:

Would you comment in these patients in regard to their response to tuberculin test or any other skin tests.

Dr. A. McGehee Harvey:

We are interested in doing this. We have completed a study in the response to a series of tests. There is no increase in positivity using fungal antigens, and chemicals to which they have not been exposed before. It looks as if when they respond, they respond with

a higher degree. You don't know with tuberculosis, and typhoid because you don't know whether the patient has been exposed to this antigen previously.

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HISTOPLASMOSIS IN PUERTO RICO

Three Cases with Infection from Common Source

Luis G. De Jesús, MD
F. Ramos Morales, MD

The problem of histoplasmosis in Puerto Rico has not been adequately evaluated, although sporadic case reports (1, 2, 3, 4), surveys (5), and mycological studies (6, 7) have been reported. A comprehensive study is needed to delineate the epidemiologic features and the clinical significance of the disease in Puerto Rico.

Histoplasmosis has been reported from all continents. In the United States the highest incidence occurs in the east-central regions where in certain areas survey findings disclose 80 percent positive reaction to the histoplasmin skin test. Comprehensive studies conducted of selected epidemics have implicated bird droppings, bat guano, abandoned poultry houses and roosting areas, farm soil or manure used as fertilizer, silos, caves, and laboratory accidents as sources of infection (8, 9, 10, 11, 12, 13, 14, 15, 16). The probability of infection is substantially increased when the contaminated material becomes airborne as occurs during excavations, demolitions, tornadoes, or mechanical dispersion of animal wastes as fertilizers.

The disease process begins with the inhalation of the pathogenic fungus. The initial lesion is a localized pulmonary granuloma which is associated with lymphadenitis of the hilar glands. Sixty five to seventy five percent of individuals infected with *Histoplasma capsulatum* fail to manifest any clinical illness (17). This sizeable proportion of infected population is only detected during specific survey studies, during the evaluation of pulmonary calcifications or during the investigations of other diseases in which skin test or serological study for histoplasmosis is included. The typical clinical picture of the acute pulmonary form usually appears one to two weeks after exposure. It is characterized by sudden onset of chills, fever, malaise, prostration, cough, pain or sensation of oppression in the chest, dyspnea and sweat. The clinical manifestations range from minimal to quite severe. The clue to the diagnosis of this non-specific clinical syndrome lies in a complete history and the awareness of the clinician of the disease.

Histoplasmosis presents a variety of clinical syndromes which have been conveniently classified in acute or chronic forms of either a pulmonary or disseminated process. Studies of acute outbreaks of histoplasmosis have shown that 25 to 35 percent of the infected individuals develop an influenza-like illness one to two weeks after exposure. These influenza-like manifestations are self-limited in the vast majority of cases. Further progression to a severe disseminated form occurs in only 0.1 to 0.2 percent of cases. The progression to a generalized form is most likely to occur in children, in elderly individuals, in patients with debilitating diseases and in persons with defi-

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cient immunological mechanisms (18, 19, 20, 21, 22).

The diagnosis of histoplasmosis is established by isolating the organism in culture media for fungus or by microscopic examination of tissues, secretions or body fluids. At times the fungus is visible in a routine peripheral blood smear or bone marrow examination. Positive cultures are usually obtained from bronchial secretions, blood, urine, bone marrow or lymph node-material. In asymptomatic and in early cases with transient pulmonary disease attempts to isolate the organism are often unrewarding. In chronic pulmonary forms of the disease the isolation rate is about 25 percent (23). Immunological procedures such as skin testing, or detection of antibodies by complement fixation or precipitin reactions provide evidence of infection. A positive skin test indicates that the patient had previously been in contact with the organism. Irrespective of any further changes in the disease process the skin test remains positive after the initial infection. Serological tests for histoplasmosis become positive during the active phases of the disease and remain positive for 6 to 12 months after cessation of activity. Studies have revealed that the administration of the skin test antigen may stimulate production of antibodies which are detectable by the serological reactions. Blood for serodiagnostic tests should be drawn before or within few days after the application of the skin test (24, 25, 26).

Histoplasma share antigens in common with other fungi such as *Blastomyces* and *Coccidiodomyces.* These common antigens are responsible for the cross reactions which are observed during immunodiagnostic procedures such as skin or serological tests. It has been documented that in most instances the degree of positivity is greater to the homologous antigen than to the heterologous antigen (27, 28).

The number of seriously ill cases of histoplasmosis requiring specific therapy is fortunately low. Most cases need only supportive treatment during the acute phase. Specific therapeutic measures are indicated in any case of progressive or disseminated disease, in persistent and symptomatic primary pulmonary infection, in chronic pulmonary disease, in persons with mucocutaneous lesions and in those known to be highly susceptible because of age, the presence of other debilitating diseases, or impaired immunological mechanisms.

Amphotericin B is the drug of choice against histoplasmosis. It has proven its value in all modalities of the disease in which specific therapeutic measures are indicated. The best effect is obtained when it is given intravenously. The total dosage and duration of therapy with Amphotericin B depends on both the type and severity of toxic reactions encountered, as well as on the clinical, radiological, and mycological response seen in the patient. If no severe adverse reactions occur it is usually administered in an intravenous infusion with increasing doses reaching up to 1 mg/kg of body weight. The total dose is generally from 2 to 3 g (29, 30). Prolonged therapy with Amphotericin B is usually necessary and side reactions are quite common, some of them potentially dangerous. Hence, Amphotericin B should be given only to hospitalized patients under close clinical observation. Most patients will exhibit some intolerance to the drug. The most frequent side effects encountered are fever, shaking chills, malaise, headache, nausea, and vomiting. If the reactions are troublesome they can be minimized or controlled by modifying the schedule of treatment or by giving aspirin, antihistaminics or both prior to the administration of the Amphotericin B. At times corticosteroids has been used to control the adverse reactions to the drug (31). Amphotericin B is nephrotoxic. It may produce

alterations in the blood urea nitrogen and serum creatinine, as well as granular and hyline urinary casts, and occasionally microhematuria. Therapy should be monitored with renal function tests and complete urinalysis. Hypokalemia is common and demands replacement therapy (32, 33). A reversible normocytic normochromic anemia has been described to occur with the administration of the drug. Thrombocytopenia has been rarely reported (34). Maculopapular rash, anaphylactoid reactions and hepatotoxicity have been also described. Other less common side effects are dyspepsia, abdominal cramps, diarrhea, melena, hemorrhagic gastroenteritis, vertigo, blurred vision, diplopia, peripheral neuropathy, and other neurological manifestations (35).

Cortisosteroids have been utilized alone in the treatment of histoplasmosis in an attempt to reduce the overwhelming toxicity associated with extensive disease but their use cannot yet be generally recommended since considerable disagreement exists (36).

This communication deals with three cases of early pulmonary histoplasmosis acquired at the Aguas Buenas caves. Investigation of the cases implicates the bat guano as the source of infection. In the present cases the patients were brought to the clinic by an alert laboratory technician who suspected the diagnosis when one of the patients mentioned the Aguas Buenas caves.

Case Reports

On February 18, 1968 three residents of continental USA toured the Aguas Buenas caves. They were lost for at least two hours during which they wandered through the place. They recall coming into close contact with bats and bat guano. The Aguas Buenas caves are known to be heavily populated by bats which over the years have left thick deposits of guano. On March 20, 1968 (31 days after exposure) the three patients were seen at the University Hospital.

Case 1:

This was a twenty nine year old male factory manager, who was born and raised in the urban area of Carlton, Georgia. The patient has travelled through South and Southeast U. S. A., and came to Puerto Rico during 1966. His first exposure to caves was during the Aguas Buenas exploration. His only symptom was lassitude which appeared 12 days after exposure and subsided spontaneously in 2 weeks. In spite of this rather asymptomatic course

TABLE I: SERODIAGNOSTIC AND SKIN TEST RESULTS

Case	COMPLEMENT FIXATION TEST TITER			SKIN TEST (mm.)			
	Histoplasmosis Yeast Phase Antigen	*Blastomycosis Yeast Phase Antigen*	*Coccidiodomycosis Myceleal Phase Antigen*	*Histoplasmin*		*Coccidiodin*	
				Erythema	*Induration*	*Erythema*	*Induration*
1	1:128	1:64	Neg.	25	15	21	12
2	1:128	1:64	1:8	50	25	33	16
3	1:128	1:64	Neg.	32	16	00	00

TABLE II: WHITE BLOOD CELL AND DIFFERENTIAL COUNTS

Case	Days after exposure	WBC per cu.mm.	Baso. Percent	Eos. Percent	Stabs Percent	Seg. Percent	Lympho. Percent	Monos. Percent
1	31	6,700	0	3	3	51	34	9
	38	8,000	1	1	11	56	25	6
	60	7,700	1	1	5	63	26	4
2	31	9,300	0	5	31	34	25	5
	38	8,050	0	3	21	58	15	3
	60	6,000	1	7	3	44	33	12
3	31	12,900	0	1	15	50	30	4
	38	12,250	1	4	9	43	42	1
	60	11,300	0	3	7	68	19	3

he was found to have radiographic evidence of acute pulmonary histoplasmosis, a positive histoplasmin skin test, and a positive histoplasma cephalin flocculation test using yeast phase antigen (Table I). Chest X-ray studies on March 21, 1968 revealed nodular infiltrates located peripherally at the 7th and 8th right intercostal spaces posteriorly and in the left posterior 8th intercostal space. Follow up films on April 19, 1968 disclosed almost complete clearing of the previously reported nodular infiltrates and a resolving nodule in the right middle lung field.

Culture for fungus from bronchial washing was negative as well as latex agglutination test with histoplasmin. The PPD, Battey, and skin test for schistosomiasis were negative. The stools failed to reveal ova or parasites. Studies on white blood cell count and differential are shown in Table II.

Case 2:

This was a thirty year old male factory supervisor who was born and raised in Illinois. The patient has travelled throughout Eastern and Southeastern U. S. A. and once vacationed in western U. S. A. and passed through the San Joaquín Valley. He moved to Puerto Rico in 1964. He never had exposure to caves before the Aguas Buenas trip on February 18. He recalls touring the caves wearing tennis shoes. The night of the trip he had severe pain in the arches of each foot and during the following days his feet became hot, red, swollen, and tender. On March 4 he was seen by a physician who diagnosed traumatic arthritis and prescribed a phenylbutazone-prednisone combination. He took the medication for five days, and his feet improved. On March 8 he noticed tender nodules in his axillae. He was advised to discontinue his deodorant and the therapy was changed to plain phenylbutazone. Next day he developed an erythematous pruritic maculopapular rash affecting mainly the face, arms, and legs. The rash was accompanied by daily chills and fever. The temperature rose during late afternoon and lasted for one week. He also noted tender fingers and described splinter hemorrhages under his nails.

The physical examination on March 20, 1968, revealed an erythematous coalescent, maculopapular rash involving his entire body. Diagnostic procedures for histoplasmosis disclosed a positive skin test and positive cephalin flocculation test using yeast phase

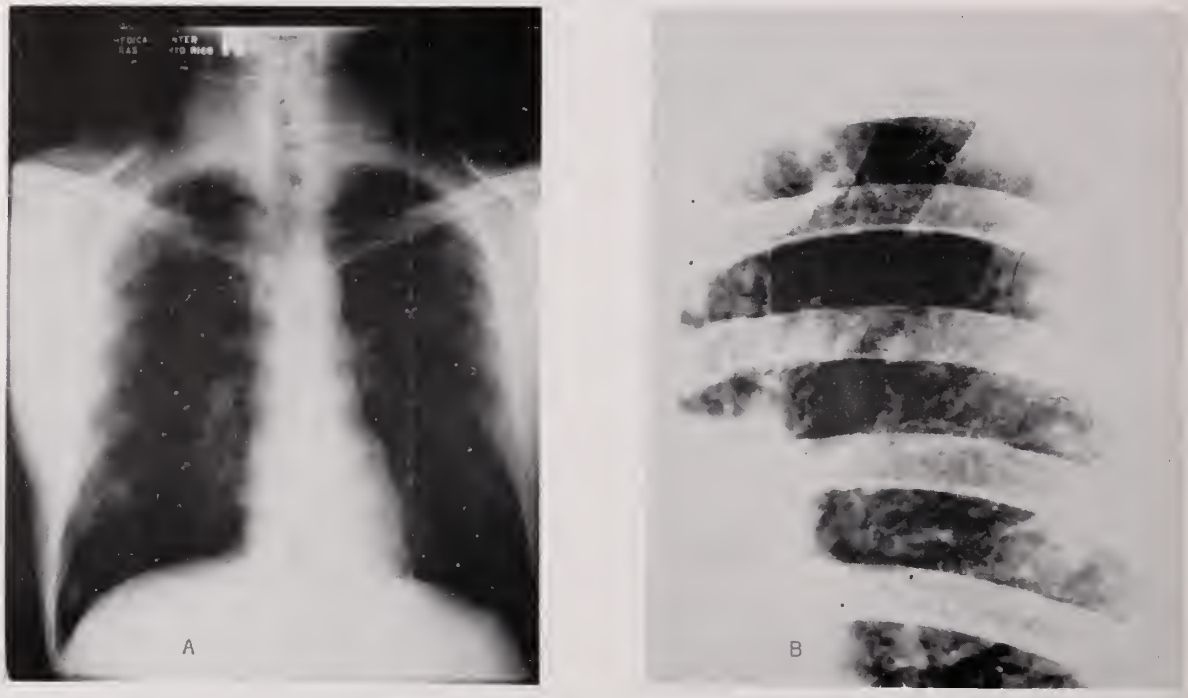


Fig. 1: Case 3. A. Chest X-ray revealing multiple discrete nodular lesions in the periphery of the lungs. B. Detail of left upper lobe shows lesions to better advantage.

antigen (Table I). The chest X-ray studies were compatible with acute pulmonary histoplasmosis. The patient recovered gradually and on April 19 he was doing well. X-ray films on March 21, 1968 show multiple discrete pulmonary nodular lesions which in some area were indistinct. These changes were seen bilaterally and involved all segments. Follow up films April 21, 1968 revealed gradual resolution of the lesions.

Bronchial washings performed on March 27, 1968 failed to grow fungus. The latex agglutination test with histoplasmin was negative. Skin test for schistosomiasis as well as Battey and PPD were negative. Stool examinations were negative for ova or parasites. White blood cell counts and differential are shown in Table II.

Case 3:

This was a twenty nine year old male factory supervisor who was born and raised in an urban area in Georgia. He had travelled through Eastern and Southeastern U. S. A., and during his Army duty he was stationed in Naples, Italy. He moved to Puerto Rico in 1963. During the night following the exploration of the caves he developed an episode of chillness and a febrile sensation which lasted a few hours. Subsequently he was well until 14 days after exposure when he started having daily fever in the late afternoon and evening, a sensation of tightness in the chest and a mild to moderate cough without expectoration. These symptoms disappeared in one week and he had been completely asymptomatic since then. As in the previously described cases he had X-ray evidence of acute pulmonary histoplasmosis and immunological tests compatible with the disease (Table I). Chest X-ray studies on March 21, 1968 disclosed multiple discrete nodular lesions seen bilaterally and peripherally. Follow up films on April 20, 1968 revealed partial resolution of the previously reported nodular infiltrates (Fig. 1).

Discussion

An outbreak of histoplasmosis affecting a group of scouts that toured the Aguas Buenas caves was reported in 1964 by Sifontes, *et al* (4). In 1966 Torres de Blasini and Carrasco reported on the isolation of *H. capsulatum* from soil and bat guano from the Aguas Buenas caves (6). The present communication on a second outbreak of histoplasmosis implicating the same site and source of infection is further proof of the health hazard that the Aguas Buenas caves represent. The public should be discouraged from visiting caves in Puerto Rico until studies in each cave have revealed that they do not represent a health hazard.

The cases presented revealed different degrees in the clinical manifestations of acute pulmonary histoplasmosis. The first case was asymptomatic in spite of the pulmonary pathological process which was demonstrated by X-ray studies. The second case had pain, swelling, redness, increased heat of the feet the night after exposure, but this cannot be ascribed to histoplasmosis. Probably this resulted from trauma to the feet related to improper foot wear. The clinical manifestations of fever, skin rash, lymphadenopathy and splinter hemorrhages which appeared two weeks after exposure are similar to those previously described in acute histoplasmosis. The possible role of phenylbutazone and steroids in the clinical picture developed by the patient can not be determined. The third case is a more typical case, with the febrile illness being accompanied by pulmonary symptoms. The symptoms in acute histoplasmosis usually appear about two weeks after exposure.

In all of the cases the diagnosis was corroborated by positive skin and serodiagnostic tests, and compatible chest X-rays findings. The three patients were followed closely and they had a rather benign course not requiring specific therapy with Amphotericin B.

Summary

The problem of histoplasmosis in Puerto Rico needs to be evaluated. The epidemiological aspects as well as the clinical features require a comprehensive survey. An outbreak affecting three individuals and implicating the bat guano in the Aguas Buenas caves is presented. A short review on the epidemiology, pathophysiology, clinical manifestations, diagnostic procedures and therapy of the disease is made. The public should be discouraged from visiting caves in Puerto Rico until studies in each cave have revealed that they do not represent a health hazard.

Resumen

Se ha presentado un brote de histoplasmosis pulmonar aguda que afectó a tres individuos. Las cuevas de Aguas Buenas fueron la probable fuente de infección. Se discuten brevemente la epidemiología, patofisiología, manifestaciones clínicas, procedimientos diagnósticos y la terapia de la enfermedad. Se aconseja el abstenerse de visitar las cuevas de Puerto Rico hasta que estudios demuestren que éstas no representan un riesgo para la salud.

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EDITORIAL

HISTOPLASMOSIS IN PUERTO RICO

The article reporting three acute cases of histoplasmosis in Puerto Rico by Guillermo de Jesús and Ramos Morales in this issue of the Boletín brings again to our attention a mycotic infection, common in Puerto Rico, which needs further evaluation in our environment from the standpoint of epidemiological studies and clinical significance.

Histoplasmosis infection as demonstrated by a positive cutaneous reaction to the histoplasmin antigen is prevalent throughout Puerto Rico. A higher percentage of infections has been found in the mountainous areas than in the coast, but reactors are found throughout the island of Puerto Rico (1). In surveys carried out by the U. S. Public Health Service Tuberculosis Research Field Center in Puerto Rico, it was found that in certain schools as many as 75 percent of the children were infected in a town like Mayagüez, while in another school in the same town very few children were found to be infected. Other epidemiological investigations at the Pediatric Chest Clinic of the University Hospital revealed situations such as that of one family living in the center of town in Villalba, all of whose members were infected and had pulmonary roentgenographic manifestations of histoplasmosis. The youngest member of the family, a ten-month old infant who had never left the area, had primary histoplasmosis. The infection seemed related to chicken coops in the patio of the household. Therefore, caves such as that of Aguas Buenas and Los Panes in Utuado are not the only source of histoplasmosis infection in Puerto Rico. However, it is likely that because of the intimate exposure and closed environment of the caves, persons exposed under those circumstances will be more heavily infected and will be more likely to show clinical manifestations. From surveys among our medical students we estimate that the overall prevalence of infection with histoplasmosis in Puerto Rico is about a 25 percent. This fact has practical importance in many respects. In the first place, pulmonary calcification in Puerto Rico cannot be interpreted as healed primary tuberculosis since, at present, a calcified lesion in the lungs of a young person who has always resided in Puerto Rico is more likely to be due to histoplasmosis than to tuberculosis. Infections with non-tuberculous mycobacteria should be another consideration, but experience has shown that non-tuberculous mycobacteria are less likely to produce calcification than tuberculosis or histoplasmosis.

The other aspect of importance is recognition of potentially fatal, chronic, or disseminated forms of the disease. Such recognition may be life saving since therapy is available with amphotericin B and sulfonamides (2). It is also important to recog-

nize the disseminated form because its clinical picture may simulate blood dyscrasias that are customarily treated with corticosteroids which may be harmful in patients with histoplasmosis unless they are receiving amphotericin B.

The role of **Histoplasma capsulatum** *in producing asthma has been misinterpreted in recent press reports concerning bat-infested classrooms. It is more likely that many of the respiratory symptoms encountered in such classrooms were due to an allergic reaction associated with bats and the classroom environment rather than to actual infection with* **Histoplasma.**

The epidemiology of histoplasmosis needs further clarification. There are a number of puzzling findings which need to be more thoroughly studied. One of these is the difficulty which we have encountered in obtaining positive cultures for **Histoplasma capsulatum** *from cave soil samples. Another puzzling finding is the rarity of obtaining positive cultures for* **Histoplasma capsulatum** *from the entire carcass of Puerto Rican bats (3). Additional studies are necessary to determine whether bats and bat droppings are actually responsible for the cave outbreaks or whether rodents or other animals might be responsible for the presence of the fungus in the caves.*

The importance of investigating the potential health hazards presented by the various caves in Puerto Rico cannot be minimized. Even if an attempt is made to close the caves it will not be possible nor practical to maintain the constant surveillance necessary to prevent cave explorers from entering the caves and becoming infected. In addition, our caves have a tremendous potential value for recreational and scientific activities which should justify further investigations concerning the degree of contamination and cost of decontamination. The U. S. Public Health Service has shown that it is feasible to decontaminate **Histoplasma capsulatum**-*infected soil by using creosole or formaldehyde solutions. This is a possibility that should be considered for histoplasmosis infected caves of Puerto Rico.*

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El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

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e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

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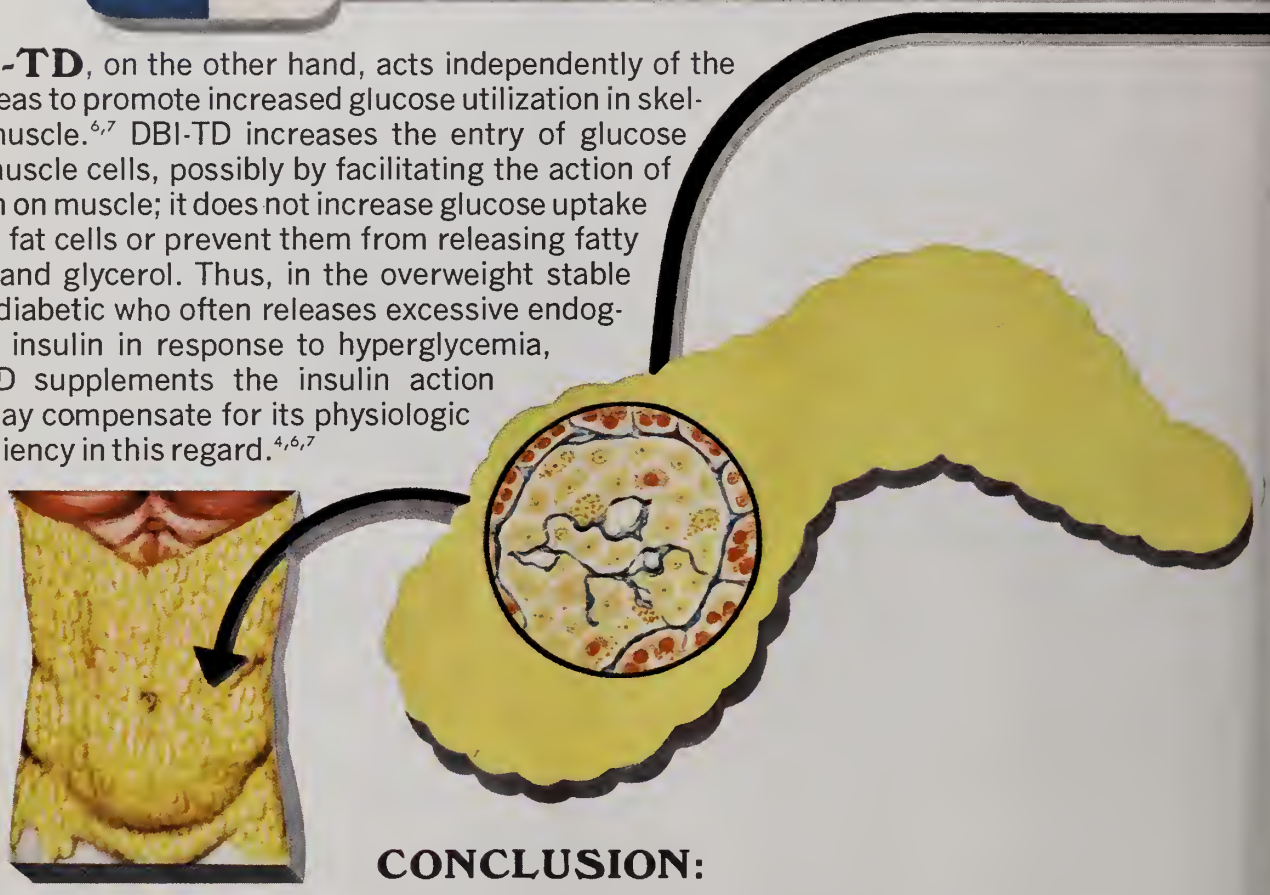
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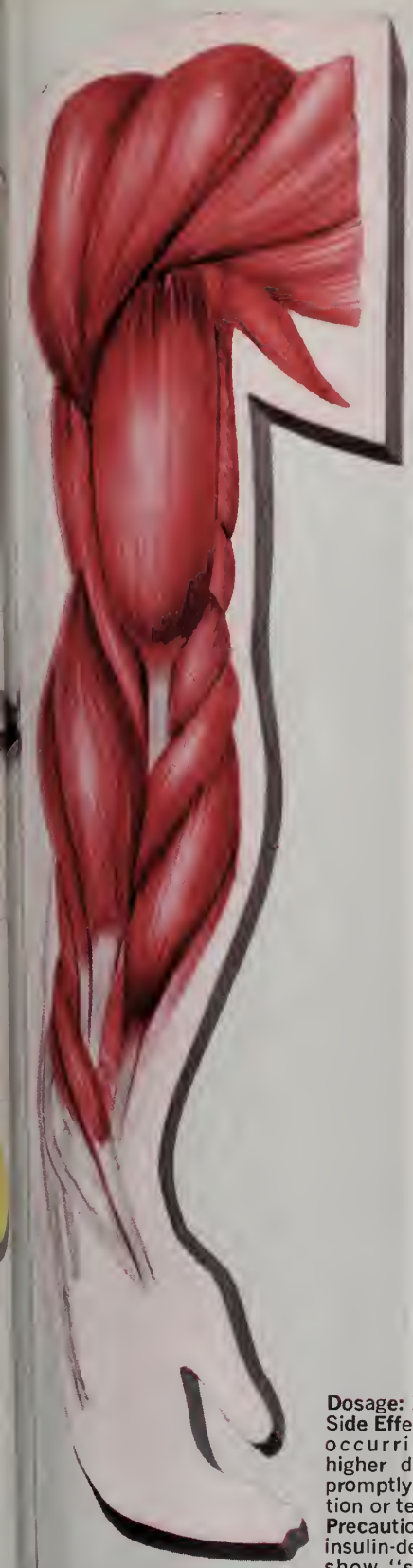
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CONCLUSION:

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Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis (ketonuria without hyperglycemia) which must be differentiated from "insulin lack" ketosis which is accompanied by acidosis, and treated accordingly. Lactic acidosis has been reported in nondiabetics and diabetics treated with insulin, with diet, and with DBI. Question has arisen regarding possible contribution of DBI to lactic acidosis in patients with renal impairment and azotemia and also those with severe hypotension secondary to myocardial or bowel infarction. Periodic B.U.N. determination should be made when DBI is administered in the presence of chronic renal disease. DBI should not be used when there is significant azotemia. Any cardiovascular lesion that could result in severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also available:** DBI tablets 25 mg. Consult product brochure.

References: 1. Yalow, R.S. and Berson, S.A.: Diabetes 9:254, 1960. 2. Grodsky, G.M. et al.: Metabolism 12:278, 1963. 3. Gundersen, K. and Antoniades, H.: Proc. Soc. Exp. Biol. Med. 104:411, 1960. 4. Williams, R.H.: Textbook of Endocrinology, Ed. 3, Philadelphia, Saunders, 1962. 5. Gordon, E.S.: Advances Internal Med. 12:66, 1964. 6. Butterfield, W.J.H. and Whichelow, M.J.: Diabetes 11:281, 1962. 7. Searle, G.L. and Cavalieri, R.R.: Presented at 26th Ann. Meet. Amer. Diabetes Ass., Chicago, June 25-26, 1966.

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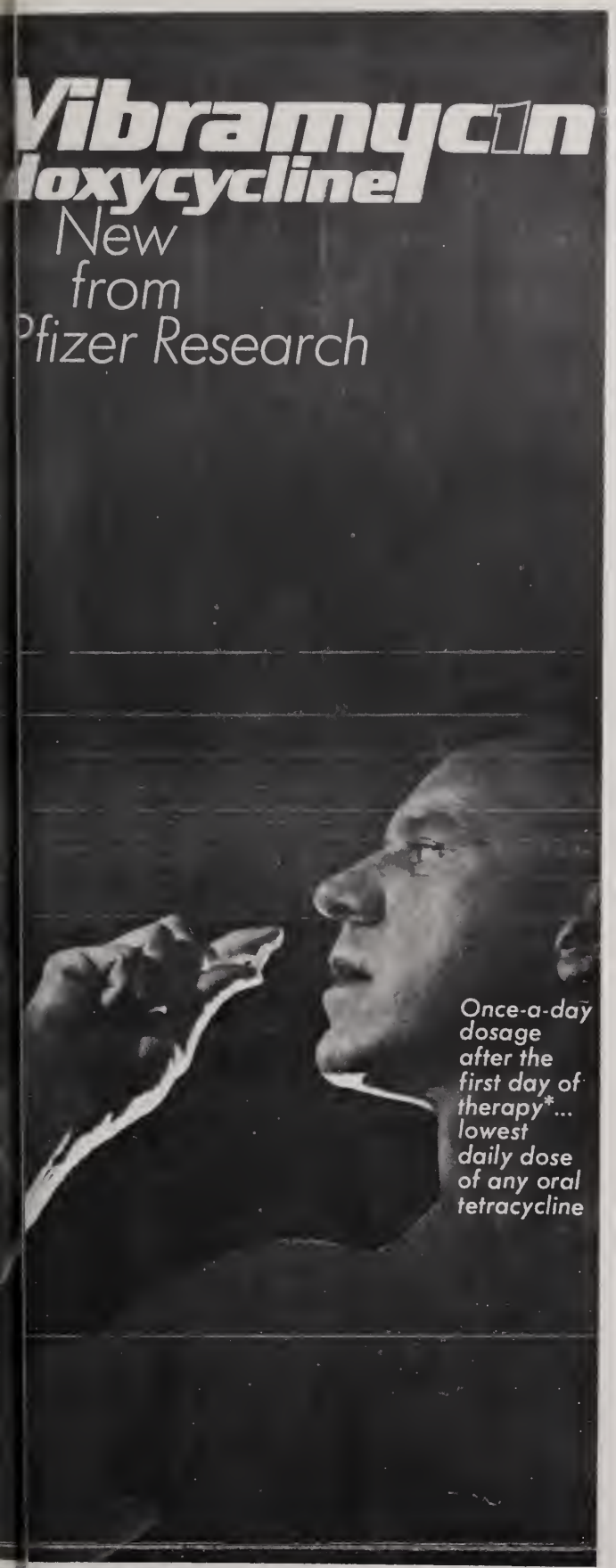
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Actions: Vibramycin (doxycycline), a new broad-spectrum antibiotic, differs from other tetracyclines in its greater absorption from the gastrointestinal tract and its capability for once-a-day maintenance dosage. Also, in comparison with certain other tetracyclines, the absorption of Vibramycin is not notably diminished by the ingestion of food or milk.

After discontinuance of therapy, effective antibacterial levels of Vibramycin are usually present for 24-36 hours.

Animal Pharmacology: As with other tetracyclines, at doses greater than those recommended for human usage, Vibramycin (doxycycline) produces discoloration of animal thyroid glands. Careful monitoring of animals and humans has disclosed no abnormalities of thyroid function studies. Also, as with other tetracyclines, at relatively high oral doses, evidence of hepatotoxicity has been noted in dogs and signs of gastrointestinal intolerance have been seen in both dogs and monkeys.

Indications: Vibramycin has been found to be clinically effective in the treatment of a variety of bacterial infections of the respiratory and genitourinary tracts and soft tissue infections. Since Vibramycin is a member of the tetracycline series, it may be expected to be useful in the treatment of gastrointestinal, ophthalmic and other miscellaneous infections when caused by susceptible organisms.

Contraindications: Vibramycin is contraindicated in individuals who have shown hypersensitivity to it.

Warnings: In patients with impaired renal function, reduce usual oral dosage and consider serum level determinations to avoid liver damage from excessive systemic accumulation.

Vibramycin, like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, although in vitro it binds calcium less strongly than other tetracyclines. The use of Vibramycin during tooth development (last trimester of pregnancy, neonatal period, and early childhood) may cause discoloration of the teeth (yellow-gray-brownish). This effect may occur mostly during long-term use, but also may occur with short-treatment courses.

Increased intracranial pressure with bulging fontanelles has been observed in infants receiving tetracyclines, which effect disappears rapidly on cessation of therapy.

In certain hypersensitive individuals treated with Vibramycin, exposure to direct sunlight may precipitate a photodynamic reaction. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. Constant observation of the patient is essential. If such superinfections are encountered, Vibramycin should be discontinued and replaced by appropriate therapy.

When treating gonorrhea in which lesions of primary or secondary syphilis are suspected, proper diagnostic procedures, including darkfield examinations, should be utilized. In all cases in which concomitant syphilis is suspected, monthly serological tests should be made for at least four months.

Adverse Reactions: Nausea, vomiting, diarrhea, vaginitis, and dermatitis, as well as reactions of an allergic nature, may occur but are rare. Glossitis, stomatitis, proctitis, onycholysis and discoloration of the nails may rarely occur during tetracycline therapy, as with other antibiotics. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

As with other tetracyclines, elevation of SGOT or SGPT values, anemia, neutropenia, eosinophilia or elevated BUN have been reported, the significance of which is not known at this time.

Dosage: The usual dose of Vibramycin is 200 mg. on the first day of treatment (administered 100 mg. every 12 hours) followed by a maintenance dose of 100 mg./day. The maintenance dose may be administered as a single dose, or as 50 mg. every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg. every 12 hours is recommended.

The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight divided into two doses on the first day of treatment, followed by 1 mg./lb. of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections, up to 2 mg./lb. of body weight may be used. For children over 100 lbs., the usual adult dose should be used.

Therapy should be continued beyond the time that symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present for 24 to 36 hours following the discontinuation of Vibramycin.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Aluminum hydroxide gel given with tetracycline antibiotics has been shown to decrease their absorption.

Supply: Vibramycin Hyclate (doxycyline hyclate) is available as capsules containing doxycycline hyclate equivalent to 50 mg. of doxycycline, bottles of 50.

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1 DATE OF FILING: October 1, 1968

2 TITLE OF PUBLICATION: Boletín de la Asociación Médica de Puerto Rico

3 FREQUENCY OF ISSUE: Monthly

4 LOCATION OF KNOWN OFFICE OF PUBLICATION *(Street, city, county, state, ZIP code)*: Asociacion Medica de Puerto Rico, Fernández Juncos Avenue 1305 Santurce, Puerto Rico - 00908

5 LOCATION OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS *(Not printers)*: Same as above

6. NAMES AND ADDRESSES OF PUBLISHER, EDITOR, AND MANAGING EDITOR

PUBLISHER *(Name and address)*: Asociación Médica de Puerto Rico - P. O. Box 9387, Santurce, P. R. 00908

EDITOR *(Name and address)*: Julio V. Rivera, MD, P. O. Box 9387, Santurce, P. R. 00908

MANAGING EDITOR *(Name and address)*: Gregorio Díaz, P. O. Box 9387, Santurce, P. R. 00908

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Contraindications: History of hypersensitivity to any component.

Warning: If renal impairment exists, even usual doses may lead to liver toxicity. Under such conditions, lower than usual doses are indicated and, if therapy is prolonged, serum level determinations may be advisable. Hypersensitive individuals may develop a photodynamic reaction to natural or artificial sunlight during use. Individuals with a history of photosensitivity reactions should avoid direct exposure while under treatment, which should be discontinued at first evidence of skin discomfort.

Precautions: Some individuals may experience drowsiness, anorexia, and slight gastric distress. If excessive drowsiness occurs, it may be necessary to increase the interval between doses. Persons on full dosage should not operate any vehicle. Use may result in overgrowth of nonsusceptible organisms. If infections appear during therapy, appropriate measures should be taken. Infections caused by beta-hemolytic streptococci should be treated for at least 10 full days to help prevent rheumatic fever or acute glomerulonephritis. Use of tetracycline during tooth development may cause discoloration of teeth.

Adverse Reactions: Gastrointestinal—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. Skin—maculopapular and erythematous rashes (a case of exfoliative dermatitis has been reported); photosensitivity; onycholysis and discoloration of nails (rare). Kidney—rise in BUN, apparently dose related. Hypersensitivity reactions—urticaria, angioneurotic edema, anaphylaxis. In young infants, bulging fontanels following full therapeutic dosage has been reported. This has disappeared rapidly when drug was discontinued. Teeth—dental staining (yellow-brown) in children of mothers given tetracycline during the latter half of pregnancy and in children given the drug during the neonatal period, infancy, and early childhood. Enamel hypoplasia has been seen in a few children. Blood—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. Liver—cholestasis (rare), usually at high dosage. If adverse reaction or idiosyncrasy occurs, discontinue medication and institute appropriate therapy.

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Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardíacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

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reserpine 0.25 mg.



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Indications: Hypertension. **Contraindications:** History of mental depression, hypersensitivity, and most cases of severe renal or hepatic diseases. **Warning:** With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has frequently been required and deaths have occurred. Discontinue coated potassium-containing formulations immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur. Discontinue one week before electroshock therapy, and if depression or peptic ulcer occurs. *Use in pregnancy:* Because chlorthalidone may cross the placental barrier and appear in cord blood and thiazides may appear in breast milk, this drug should be used with care in pregnant patients and nursing mothers. When used in women of childbearing age, the potential benefits of the drug should be weighed against the possible hazards to the fetus. Use of chlorthalidone may result in fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. Increased respiratory secretions, nasal congestion, cyanosis and anorexia may occur in infants born to reserpine-treated mothers. **Precautions:** Antihypertensive therapy with this drug should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs, or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. To avoid hypotension during surgery, discontinue therapy with this agent two weeks prior to elective surgical procedures. In emergency surgery, use, if needed, anticholinergic or adrenergic drugs or other supportive measures as indicated. Because of the possibility of progression of renal damage, periodic kidney function tests are indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated. Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, the drug should be discontinued and potassium supplements given, provided the patient does not have marked oliguria. Take particular care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Severe salt restriction is not recommended. Use cautiously in patients with ulcerative colitis or gallstones (biliary colic may be precipitated). Bronchial asthma may occur in susceptible patients. **Adverse Reactions:** The drug is generally well tolerated. The most frequent side effects are nausea, gastric irritation, vomiting, diarrhea, constipation, muscle cramps, headache, dizziness and acute gout. Other potential side effects include angina pectoris, anxiety, depression, bradycardia and ectopic cardiac rhythms (especially when used with digitalis), drowsiness, dull sensorium, hyperglycemia and glycosuria, hyperuricemia, lassitude, restlessness, transient myopia, impotence or dysuria, orthostatic hypotension which may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics, leukopenia, aplastic anemia, skin rashes, thrombocytopenia, agranulocytosis, nasal stuffiness, increased gastric secretions, nightmare, purpura, urticaria, ecchymosis, weakness, uveitis, optic atrophy and glaucoma, and pruritus. Eruptions and/or flushing of the skin, a reversible paralysis agitans-like syndrome, blurred vision, conjunctival injection, increased susceptibility to colds, dyspnea, weight gain, decreased libido, dryness of the mouth, deafness, anorexia, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Jaundice, xanthopsia, paresthesia, photosensitization and necrotizing angiitis are possible. **Average Dosage:** One tablet daily with breakfast. **Availability:** Pink, single-scored tablets in bottles of 100 and 1000.
(B)46-600-C

For details, please see complete prescribing information.

Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York 10502

RE-6225



para esa tos molesta recomiende el nuevo jarabe, sin narcóticos

Cheracol D

dominio efectivo de la tos, sin codeína

Cheracol D con dextrometorfano:

- acción antitusiva igual que con codeína, pero sin efectos secundarios narcóticos indeseables
- afloja las secreciones bronquiales
- refresca y suaviza la garganta
- tiene un agradable sabor a cerezas que lo hace muy popular entre los niños
- puede ser administrado a niños menores de dos años, bajo la vigilancia del médico

Cada onza fluida contiene:

Bromhidrato de dextrometorfano	9/10 gr. (60 mg.)
Cloroformo*	2 grs.
Guayacolato de Glicerilo	1⅖ grs.
Cloruro de Amonio	8 grs.
Tartrato de Antimonio y Potasio	1/12 gr.
Alcohol	3%

con corteza de pino blanco y de cerezo silvestre

*Cierta pérdida de cloroformo es inevitable.

Presentación: en frascos de 2 y 4 onzas.

Upjohn

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UPJOHN INTER-AMERICAN CORPORATION/CAPARRA/PUERTO NUEVO

ready for bed..



but not for sleep

...because psychic tension may not stop at night

The calming action of Valium (diazepam) helps counteract psychic tension and reduce overreaction to stresses during the day. Often the t.i.d. dosage schedule is enough to prevent build-up of tenseness that may interfere with sleep at night.

However, when psychic tension does contribute to sleeplessness, Valium can be especially useful. A tablet at bedtime, added to the daytime t.i.d. dosage, can help your patient be ready for bed *and* for sleep.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or wi suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclu ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplop hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurre speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such acute hyperexcited states, anxiety, halluci tions, increased muscle spasticity, insomn rage, sleep disturbances, stimulation, have been reported; should these occur, discon tinue drug. Isolated reports of neutropenia jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Valium®
(diazepam)

ROCHE

Roche®
LABORATORIES

Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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ESCUELA DE MEDICINA UNIVERSIDAD DE PUERTO RICO

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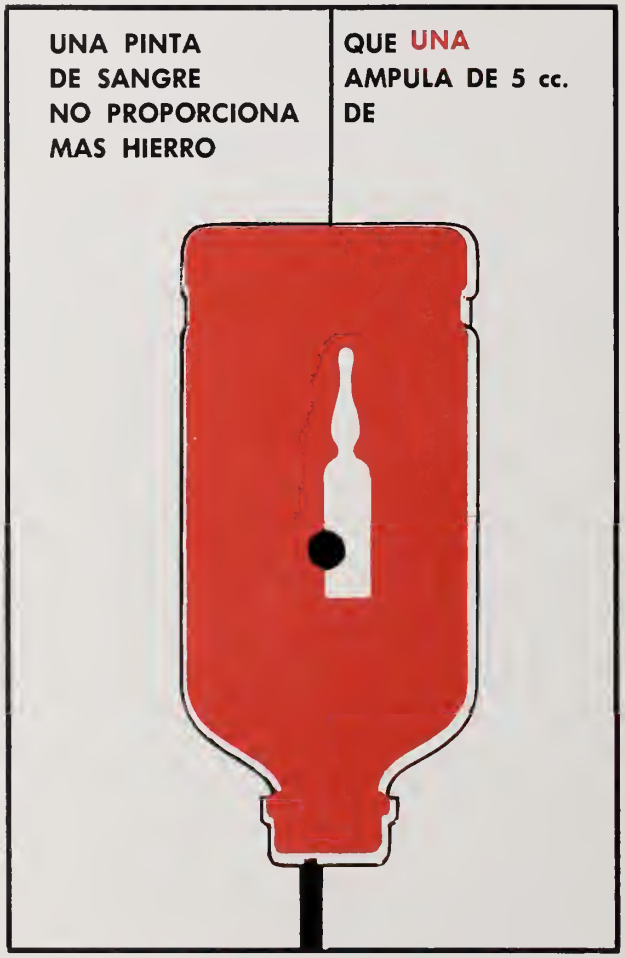
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11 MAR 1969

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Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

LAKESIDE

PRODUCTOS
PARA PACIENTES
QUE UD. VE
A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.



Lets you fit the formula to the infant

Carnation Evaporated Milk is not a rigid, ready-made infant formula. ▪ You choose the kind and amount of carbohydrate to be added. ▪ You specify the dilution with water. ▪ You maintain the right to prescribe the vitamin preparation of your choice. ▪ And you make the decision whether supplemental iron is needed. ▪ You fit the formula to the infant.

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Specify Carnation Evaporated Milk and you specify Carnation quality.

From a world leader in nutritional research . . . Carnation®

A dilemma of the aged



Whitman's malady. In 1858, three years after publishing *Leaves of Grass,* Walt Whitman suffered "a mild seizure and he recovered so rapidly that he always thought it was sunstroke."[1] From then on his life was a succession of similar events—'silent' strokes—punctuated by big strokes. In between, "...spells of fainting and very bad feeling in my head, fullness and pain...bad spells, dizziness in the head."[2]

Were Whitman's prodromal episodes transient cerebral ischemia—resulting from vasospasm? Who can know for sure? The great Osler's initial observation of the poet was: "...There was nothing serious the matter—a transient indisposition which had passed away..."[2] A Dr. Grier said Whitman's "real disease is the brain not being properly furnished and nourished with blood..."[2] And there has been a long-held view that the instantaneous onset of such episodes, and their rapid disappearance without apparent residue, are compatible with a concept of cerebral vasospasm.

1. Page, I.H., *et al.:* Strokes, New York, Dutton, 1961, p. 11. 2. Feinberg, C.E.: Arch. Intern. Med. *114*:834, Dec. 1964.

transient cerebral ischemia
(due to vasospasm)

Patients often awake with a headache, memory loss, dizziness or confusion

Although transient cerebral ischemia may develop at any time, it often occurs at night. Its victims may awake the next day dizzy and confused, or temporarily incapacitated. A cerebral vasodilator may help relieve the ischemic syndrome due to arterial spasm. But if vasodilation is to provide adequate protection against recurrent episodes, it must maintain vital blood flow even while the patient sleeps.

Cerespan q.12 h. helps protect the patient— even while he sleeps

Cerespan combines the time-tested vasorelaxant properties of papaverine with the dependable sustained action of the micro-dialysis process. The hundreds of tiny micro-dialysis cells in each Cerespan capsule require only the presence of fluid for activation. Drug release is smooth and continuous, and does not depend on G.I. functions, which are frequently unpredictable. Cerespan q. 12 h., with its prolonged action, helps protect the patient day *and* night.

A micro-dialysis product

Each Cerespan capsule contains papaverine HCl 150 mg. in micro-dialysis cells. Class M Narcotic. **Indications and Dosage:** For relief of cerebral and peripheral ischemia associated with spasm, 1 capsule *q.12 h.* **Precaution:** Use with caution in glaucoma. **Side Effects:** Rare; those reported include anorexia, nausea, abdominal distress, constipation, malaise, drowsiness, vertigo, sweating and headache.

Cerespan™
(PAPAVERINE HCl) q.12 h.

USV PHARMACEUTICAL CORP., New York, N.Y. 10017
PRODUCERS OF DBI®-TD (phenformin HCl), ARLIDIN® (nylidrin HCl)



PIENSE EN SU MEDICO Y PIENSE EN LOS SUYOS

Adquiera Tranquilidad: Ingrese en la Triple S

Nadie es eternamente saludable. Es lógico suponer que, en cualquier momento, algunos de sus familiares —o usted mismo— requerirá atención médica y, quizás, hospitalización.

Como jefe de familia, usted se verá en la obligación de atender esa necesidad con mayor premura que las otras: casa, comida, ropa, vestidos y diversiones.

No espere ese momento; adquiera tranquilidad desde ahora con el plan de protección médico quirúrgico y de hospitalización de la Triple S (SSS). Económico, eficaz y simple.

Por una módica prima mensual —menos de lo que gasta en cosas menos importantes que la salud— usted se protege y protege a los suyos. La Triple S le ofrece servicios médicos, de hospitalización y dentales.

Por eso — le aseguramos— adquirir su tarjeta de la (SSS) es adquirir tranquilidad.

Miembro de la National Association of Blue Shield Plans

®

A once-popular treatment for back pains was to have the seventh son of a seventh son stand or walk on the patient's back.





The pain of earache was allegedly relieved by holding a hot roasted onion to the ear.

or headache, a sovereign remedy was wear a snakeskin round one's head.



A realistic approach to pain relief



'Empirin'®

Compound with Codeine Phosphate gr. 1/2 No. 3

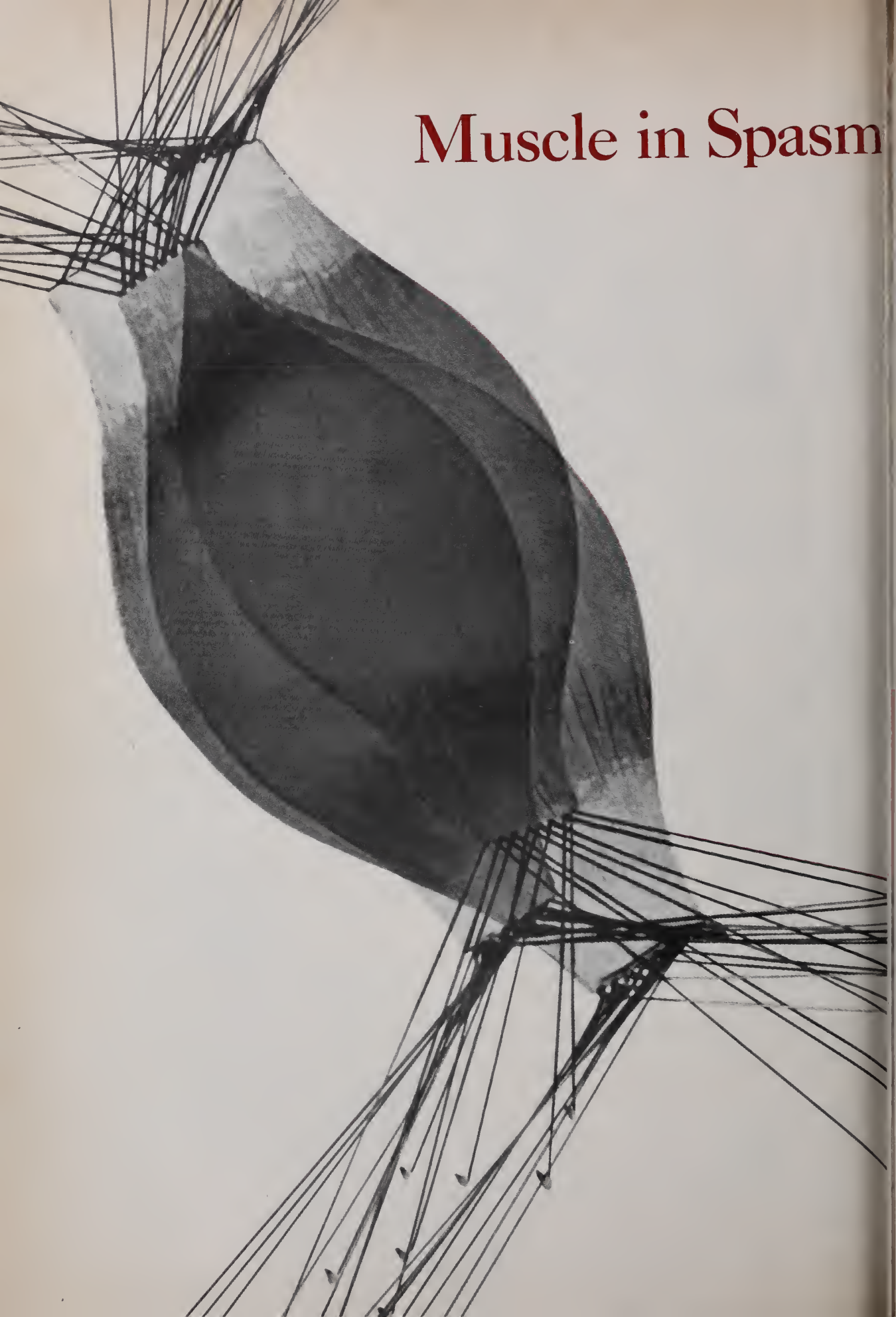
Each tablet contains:
Codeine Phosphate gr. 1/2 (Warning—May be habit forming), Phenacetin gr. 2 1/2, Aspirin gr. 3 1/2, Caffeine gr. 1/2.

keeps the promise of pain relief

'B.W. & Co.' narcotic products are Class "B", and as such are available on oral prescription, where State law permits.

BURROUGHS WELLCOME & CO. (U.S.A.) INC.
Tuckahoe, N.Y.

Muscle in Spasm



and Valium (diazepam)

The ability of Valium to help relieve skeletal muscle spasm—as well as psychic tension—demonstrates its clinical value and versatility.

The muscle-relaxant effect obtained with Valium, used adjunctively with other drugs or physiotherapy, favorably affects the entire cluster of spasm-related symptoms . . . helps accelerate return to normal activity.

When skeletal muscle spasm and psychic tension coexist, the calming effect of Valium is an added therapeutic benefit that contributes to the total management of the patient.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Valium® (diazepam)
2-mg, 5-mg, 10-mg tablets

ROCHE
Roche®
LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



A littl

Just one 50 or 100 n
tablet in the mornin
can work a long
diuretic day in eden
and hypertension.

HY-6060



Hygroton® can work a long day too
Chlorthalidone

has because of its prolonged action, which usually provides smooth diuretic activity throughout the day. And one-day dosage means few tablets to take and few tablets to pay for in the long run.

Hygroton, brand of chlorthalidone, may mean troublesome side effects for certain patients. And you can't prescribe it in cases of demonstrated hypersensitivity to the drug or in severe renal or hepatic diseases.

Before writing it for your patients, please check the Prescribing Information. It's summarized on the next page.

Hygroton
Chlorthalidone in edema and hypertension

Geigy



in edema and hypertension

A little Hygroton® can work a long day

chlorthalidone

Indications: Hypertension and many types of edema involving retention of salt and water.

Contraindications: Hypersensitivity and most cases of severe renal or hepatic diseases.

Warning: With the administration of enteric-coated potassium supplements, which should be used only when adequate dietary supplementation is not practical, the possibility of small-bowel lesions (obstruction, hemorrhage, and perforation) should be kept in mind. Surgery for these lesions has been required frequently and deaths have occurred. Discontinue enteric-coated potassium supplements immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.

Use with caution in pregnant women and nursing mothers since the drug may cross the placental barrier and appear in cord blood and since thiazides may appear in breast milk. The drug may result in fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. When used in women of childbearing age, balance benefits of drug against possible hazards to fetus.

Precautions: Antihypertensive therapy with this drug should always be initiated cautiously in postsympathectomy patients and in patients receiving ganglionic blocking agents, other potent antihypertensive drugs or curare. Reduce dosage of concomitant antihypertensive agents by at least one-half. Because of the possibility of progression of renal damage, periodic determination of the BUN is indicated. Discontinue if the BUN rises or liver dysfunction is aggravated. Hepatic coma may be precipitated.

Electrolyte imbalance, sodium and/or potassium depletion may occur. If potassium depletion should occur during therapy, the drug should be discontinued and potassium supplements given, provided the patient does not have marked oliguria.

Take special care in cirrhosis or severe ischemic heart disease and in patients receiving corticosteroids, ACTH, or digitalis. Salt restriction is not recommended.

Adverse Reactions: Nausea, gastric irritation, vomiting, anorexia, constipation and cramping, dizziness, weakness, restlessness, hyperglycemia, glycosuria, hyperuricemia, headache, muscle cramps, orthostatic hypotension, which may be potentiated when chlorthalidone is combined with barbiturates, narcotics or alcohol, aplastic anemia, leukopenia, thrombocytopenia, agranulocytosis, impotence, dysuria, transient myopia, skin rashes urticaria, purpura, necrotizing angiitis acute gout, and pancreatitis when epigastric pain or unexplained G.I. symptoms develop after prolonged administration. Other reactions reported with this class of compounds include: jaundice, xanthopsia, paresthesia, and photosensitization.

Average Dosage: 50 or 100 mg. with breakfast daily or 100 mg. every other day.

Availability: White, single-scored tablets of 100 mg. and aqua tablets of 50 mg., in bottles of 100 and 1000.

(B)46-230-E

For full details, please see the complete prescribing information.

Geigy Pharmaceuticals
Division of
Geigy Chemical Corporation
Ardsley, New York 10502

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Anuncios y Suscripciones:

El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

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Second class postage paid at San Juan, Puerto Rico.



NORPRAMIN
(clorhidrato de desipramina)

el ANTIDEPRESIVO
no-sedante de acción rápida

vence el abatimiento, levanta el ánimo, restablece la confianza

La depresión frecuentemente se caracteriza por sentimientos de culpabilidad, inutilidad, desolación y privación. Estas manifestaciones, acompañadas de síntomas tales como insomnio, malestar, tristeza y recelo, responden rápidamente al NORPRAMIN (clorhidrato de desipramina). La mejoría generalmente se manifiesta 2 a 5 días después de iniciado el tratamiento; algunas veces antes. Los pacientes con sensibilidad comprobada a estimulantes del sistema nervioso central, pueden experimentar excitación al desaparecer su depresión; en estos casos se sugiere reducir la dosis o administrar simultáneamente tranquilizantes.

Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardiacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

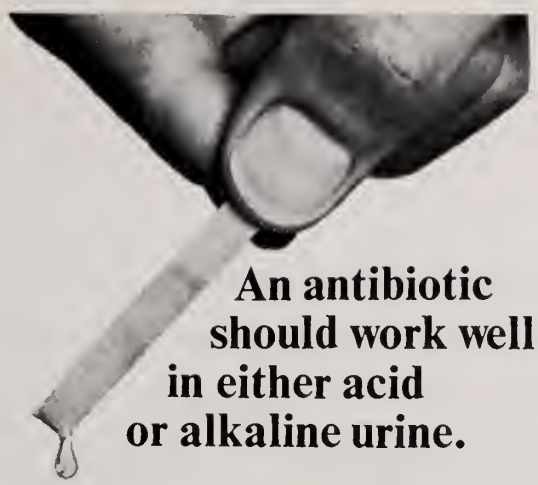
Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extraoiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

LAKESIDE

PRODUCTOS
PARA PACIENTES
QUE USTED
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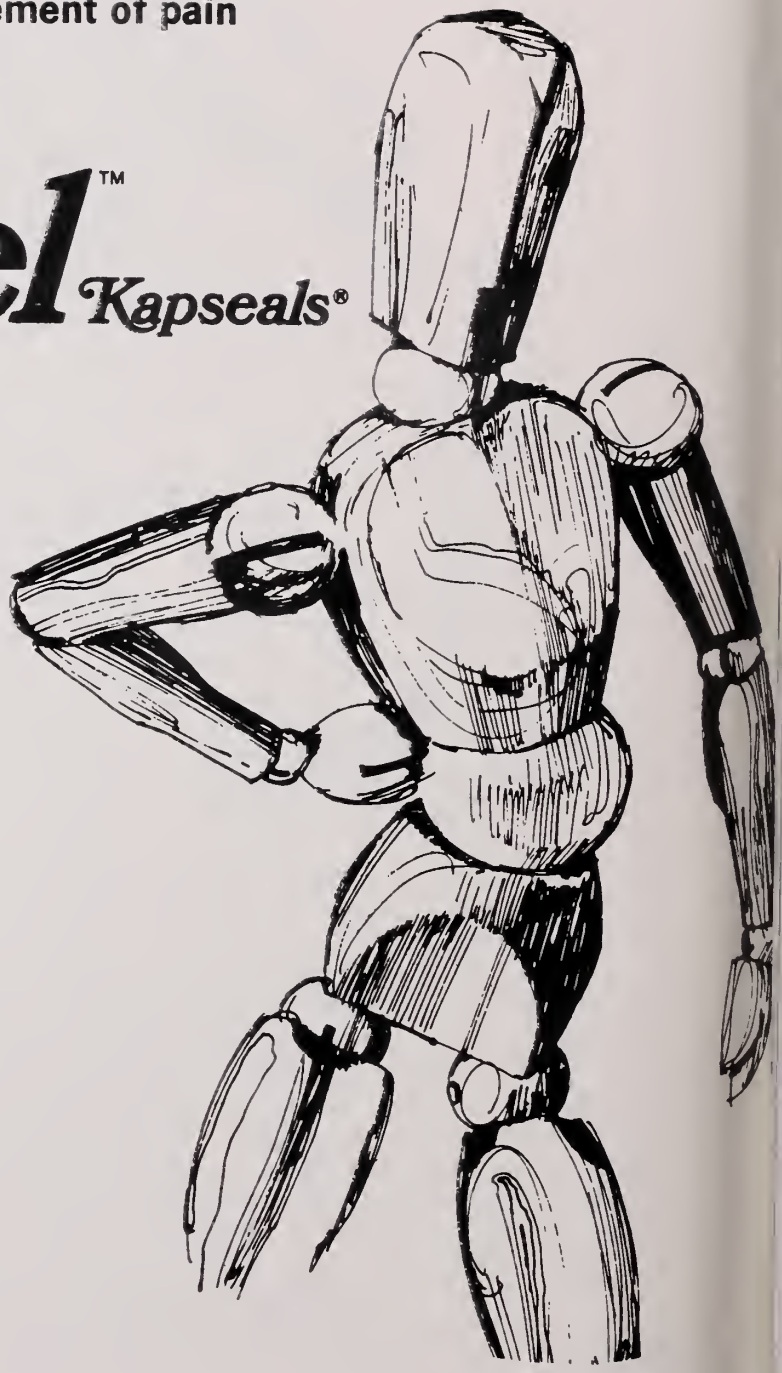
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PARKE-DAVIS

LEUKEMIA IN PREGNANCY

Julio E. Lergier *

Leukemia in pregnancy is a rare occurrence. Since Cameron in 1888 described a case of chronic myelocytic leukemia in a pregnant woman there are about 284 cases reported in the world literature up to 1967. In spite of its rarity, the occurrence of leukemia in pregnancy, specially the acute type, may present the obstetrician with difficult management problems, as exemplified by the fact that of 4 cases of acute leukemia in pregnancy seen at UDH and SJCH during the period 1964-1967 three terminated in maternal and fetal deaths. It is the purpose of this paper to present these 4 case reports, review the literature on this subject up to 1967 and discuss some of the important aspects of it, with special reference to management.

Case Reports

Case 1:

A 20-year old white Grava 0, Para 0 was referred to the Hematology Clinics of UDH in June 1964 with a history of petechiae in the thighs and wrists, generalized weakness, headaches and dizziness on standing of one month duration. At the time WBC were 186,000/cu.mm, mostly blast forms, hemoglobin was 11.1 g/100 ml, platelets were 60,000/cu.mm and the bone marrow revealed a monotonous pattern of undifferentiated white blood cell precursors. A diagnosis of acute undifferentiated leukemia was made and the patient was started on 150 mg of 6-mercaptopurine (6MP) and 60 mg of prednisone daily one month after the onset of illness.

Within two weeks the WBC count had fallen to 3,900/cu.mm and platelets were 94,000/cu. mm; on the basis of the response a diagnosis of acute lymphoblastic leukemia without a bone marrow remission was made and the patient was discharged on 75 mg of 6-MP and 15 mg of prednisone daily. An attempt at withdrawal of 6-MP resulted in exacerbation of the process and doses of 100-150mg daily were again given. Three and a half months after the onset of illness the patient was admitted with amenorrhea since June 9, 1964 and was found to be 8-10 weeks pregnant. At the time she had purpura, painful cervical lymphadenopathy, gingival swelling, sore throat and fever. WBC were 4150/cu.mm, platelets were 5000/cu.mm and hemoglobin was 8.8 g/100 ml. 6-MP was discontinued and prednisone increased to 60mg daily with addition of pennicillin and streptomycin. Twelve and 22 days after admission doses of 2 and 3mg intravenously respectively of Vincristine were given.

Twenty eight days after admission the patient had vaginal bleeding and WBC were 950/cu.mm, and platelets 4,000/cu.mm. Prednisone was increased to 250 mg daily and blood transfusions were given, but patient insisted in going home and was discharged on 280 mg of prednisone and 1 g of chloramphenicol daily as a "terminal case".

Four and a half months after the onset of illness the patient received a total of 1000r of X-radiation to the gums for painful leukemic infiltrates of the gums. Five months after onset of illness patient was admitted for the third time with vaginal spotting. Platelets had increased to 154,000/cu.mm and WBC were within normal except for 2 percent blasts; fibrinogen was 430mg/100 ml and

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the clotting time was 22 minutes. The patient was considered improved and prednisone was decreased to 80 mg daily. Five days after admission the patient had a complete abortion with hemorrhage, treated with pitocin and blood transfusions. Fetus and placenta weighed 4 kg and revealed no significant abnormalities. After the abortion the patient was discharged of her own accord. Her condition deteriorated in spite of vigorous therapy with 6-MP, methotrexate and prednisone, and she expired 6 months after the onset of illness. No post-mortem examination was done.

Case 2:

A 25-year old white Grava 2 Para 1, AbO, Neonatal death 1, was admitted January 12 1967 with an EDC of March 30, 1967, with the main complaint of bleeding from the gums of 2 months duration and purpura of 2 weeks onset. On physical examination there was gum bleeding, ecchymoses of the lower extremities and no hepatosplenomegaly. The uterine fundus was 3 cm above the umbilicus, with 8 percent blasts, platelets were 22,000/cu.mm, hemoglobin 8.8 g/100 ml and the bone marrow revealed acute granulocytic leukemia of the promyelocytic variety. Prednisone, 100mg, daily was started, but patient continued to deteriorate requiring repeated whole blood and platelets transfusions. Nine days after admission WBC were 2,400/cu.mm with 70 percent blasts, hemoglobin 11.4 g/100 ml, platelets were 11,250/cu.mm, with incomplete clot retraction, and decreased platelets adhesiveness and agglutination. Prothrombin time was normal. Serum fibrinogen was 212 mg/100 ml and fibrinolysin titers were 88.8 percent (normal 16 percent) with shortened euglobulin lysis time: 30 minutes/40 minutes control. Epsilon-aminocaproic acid, a total amount of 24 g was given intravenously in 24 hours with no reduction of elevated fibrinolysin titers. Fourteen days after admission gross hematuria developed: on the next day respiratory distress, hemoptysis and right lung base consolidation were noted which was confirmed by X-rays. A pleural tap was dry. In spite of oxygen and antibiotics, the patient deteriorated and died 2 1/2 months after the onset of illness. No post mortem examination was done.

Case 3:

A 24-year old mulatto Grava 3, Para 2, Ab O with last menstrual period August 20, 1967, admitted on October 6, 1967 with a three week history of epigastric pain and vomiting, followed by severe arm and leg pain, vaginal bleeding and soft watery chocolate colored stools. She had amenorrhea and a pregnancy test was positive. On admission she was markedly toxic and dehydrated, had generalized myalgias, bloody, chocolate diarrhea, soft blue cervix with 8-10 weeks size uterus but no hepatosplenomegaly or purpura. Temperature was 39.8° C. Initial diagnosis was Gram negative septicemia with dehydration. However, the hemoglobin was 5.3 g/100 ml, hematocrit was 13 percent and on the peripheral smear no platelets were seen and there were only 3-6 WBC per smear counted. A bone marrow done after repeated dry taps revealed no megakaryocytes, granulocytic shift to the left and several reticular cells. A repeat bone marrow showed a suspension of cells with many inmature cells, strongly suggestive of acute myeloblastic leukemia. A bone marrow biopsy 3 days after admission revealed infiltration by mononuclear cells, compatible with a malignant process, probably leukemia, but specific cell type could not be determined. The patient was treated with Ampicillin®, whole blood and platelets transfusions. Eleven days after admission 150 mg of 6-MP and 60 mg of prednisone were started. Three weeks after admission the hemoglobin was up to 6.9 g/100 ml. Vincristine, 1 mg intravenously was given and repeated 6 days later. One month after admission WBC were 100/cu.mm cells of the lymphocytic series and the platelets were very low. The patient was febrile and with gastrointestinal tract bleeding. Platelets were low and fibrinogen was 566 mg/100 ml; however, clotting, bleeding and prothrombin times were not done. 6-MP was discontinued, prednisone was decreased to 20 mg daily and 100 mg of oxymethalone (Adroyd®) daily were started because of the pancytopenia. After having received several blood transfusions the patient became severely jaundiced and disoriented and the hemoglobin fell to 4.5 g/100 ml. The patient died 8 weeks after the onset of her illness. In the post-mortem there was evidence of tubular necrosis, multiple infarcts and hemorrhages in the bone marrow and no conceptus was found in the uterus, although there was a decidual reaction with hemorrhage in the endometrium. The cause of death was considered to be secondary to an adverse blood transfusion reaction.

Case 4:

A 26-year old white Grava 3 Para 2 Ab O was

admitted on November 2, 1967 to labor room for delivery after 9 months normal gestation. In December 1962 she had the onset of weakness, and weight loss and she was seen by a physician who found neutropenia. By April 1963 she had developed generalized painful lymphadenopathy, menorrhagia and petechiae. Five months after the onset of illness WBC were 1650/cu.mm, hemoglobin 12.7/100 ml, platelets were 96,000/cu.mm and the bone marrow revealed acute lymphoblastic leukemia. She was placed on a maintenance dose of 50 mg of 6-MP and 10 mg of prednisone daily. She continued doing well until 49 months after the onset of illness when she developed a tender mass in the RLQ and few shotty cervical and axillary lymph nodes. A gynecological examination was normal. An intravenous pyelogram revealed a mass displacing the distal third of the left ureter. A bone marrow was compatible with complete remission and the peripheral smear was normal. It was considered that she was having a local tumoral mass growth. Prednisone was increased to 60 mg daily and one month later intravenous pyelogram showed decrease in the size of the mass. Fifty three months after the onset of her illness she noted amenorrhea for 37 days and a pregnancy test was positive. She had been on a dose of 50 mg of 6-MP and 40 mg of prednisone daily at the time of conception. Prednisone was decreased to 20 mg daily by the third month of gestation and 50 mg of 6-MP were continued throughout the uneventful prenatal course. On admission to labor room WBC, platelets were adequate. Four days after admission she was delivered spontaneously of a full term baby without complications -61 months after the onset of illness. Two months later an exploratory laparotomy was done and no evidence of an abdominal mass was found. Both mother and child are doing well until the present time, 66 months after the onset of illness.

Table I summarizes the most important data on these patients.

Discussion

For the years 1964-67 there were 4 cases of acute leukemia amongst approximately 112,000 cases of termination of pregnancy in the regions serviced by the University District and San Juan City Hospitals. Yahia (37) in 1958 reported 2 cases in 75,000 deliveries. Up to 1958 a total of 153 cases of leukemia in pregnancy were reviewed by Sheehy (29). For the period 1958-67 a review of the English literature (9, 13, 20, 25, 35), and our 4 case reports yield a net total of about 86 reported cases of leukemia in pregnancy (See Table II).

Table II shows the comparative distribution of various types of leukemia in pregnancy for periods up to 1958 and 1958-67. The relative incidence of chronic granulocytic leukemia has decreased, while that of acute leukemia has increased in the period 1958-67.

Mean age in our 4 cases is 23.8 years with a range of 20-26 years as compared to that reported previously (20, 22, 37) of 28 years for acute leukemia in pregnancy.

Three of our cases are white and one is mulatto. Hoover (20) reported 87 percent Caucasians and 13 percent Negroes for acute leukemia in 1964, which is the same ratio as that of the American population.

Table III shows the difference in onset as related to pregnancy for the acute as compared with the chronic leukemias for the years 1954-67. In 60 percent of cases of acute leukemia the onset was in the second or third trimester of gestation, as compared to 73 percent of cases of chronic leukemia which had their onset prior to conception. In our cases two had their onset before gestation, one in the second and one in the third trimester of pregnancy.

Table IV summarizes the different modes of therapy with corresponding fetal and maternal outcomes for 52 cases of acute leukemia in pregnancy during the period 1964-67. Total fetal mortality was 32.5 percent, compared to 60 percent to 1943 –McGoldrick and Lapp– (22) and 38.7 percent in 1943-56 –Yahia– (37). The incidence of prematurity was 17.5 percent, lower than that reported in 1943 (22) and 1958 (37), when premature labor was most common and the average length of

TABLE I: ACUTE LEUKEMIA IN PREGNANCY AT UNIVERSITY DISTRICT HOSPITAL AND SAN JUAN CITY HOSPITAL, 1964–67

Patient	Age	Gravity & Parity	Diagnosis *	Onset	Duration of Gestation	Complications	Therapy	Outcome		Duration of Disease
								Fetal	Maternal	
1	20	GIPO	ALL	1 month prior to gestation	3 1/2 mo.	Vaginal bleeding Sepsis ?	6-MP Prednisone Vincristine Radiotherapy	Aborted 3 1/2 mo (unspecific conceptus changes)	Died 1 month after abortion	6 months
2	25	G2P1	AGL	5 1/2 mo. of gestation	8 months	Bleeding Pneumonia	Prednisone EACA Platelet transf. Blood transf.	Death in utero at 8 months	Died at 8 mo. of gestation	2 1/2 months
3	24	G3P2	AGL	1 mo. of gestation	2 months	Bleeding Septicemia Blood transfusion reaction	6-MP Prednisone Vincristine Oxymethalone Blood transf.	? Abortion (no conceptus in post-mortem)	Died at 2 mo. of gestation	7-8 weeks
4	26	G3P3	ALL	52 mo. prior to gestation	9 months	None	6-MP Prednisone	N.S.D. Full term doing well at 5 mo. age	Alive, doing well 5 mo. post-partum	66 months (in remission)

* *ALL - Acute lymphoblastic leukemia*
AGL - Acute granulocytic leukemia
NSD - Normal spontaneous delivery

TABLE II: COMPARISON OF ACUTE AND CHRONIC LEUKEMIA IN PREGNANCY

Period	CGL *	CLL	AGL	ALL	AML	BLAST CELL	ERYTHRO.	MIXED	TOTAL
Up to 1958: Shechy (29)	89(54.2 percent)	4(2.4 percent)	37(23.7 percent)	16(9.7 percent)	7(4.3 percent)	0	0	0	153
1958-67: Maloney (25)	22	0	28	8	6	4	2	1	71
Hoover (20)	0	0	0	3	2	0	0	0	5
Cutting (9)	0	0	0	1	0	0	0	0	1
Dugdale (13)	4	0	0	0	0	0	0	0	4
Williams (35)	1	0	0	0	0	0	0	0	1
Present Communication	0	0	2	2	0	0	0	0	4
Total 1958-67	27(31.4 percent)	0	30(34.8 percent)	14(16.2 percent)	8(9.3 percent)	4(4.9 percent)	2(2.3 percent)	1(1.1 percent)	86

* *CGL: Chronic granulocytic, CLL: Chronic lymphocytic, AGL: Acute granulocytic, ALL: Acute lymphoblastic, AML: Acute monocytic, ERYTHRO.: Erythromyelogenous*

TABLE III: ONSET OF LEUKEMIA *

	Trimester					
Type	*Before Conception*	*First*	*Second*	*Third*	*Post Partum*	*Total*
Acute (1954-67)	10 (14.6)	10 (14.6)	27 (39.7)	14 (20.5)	7 (10.6)	68 100 percent
Chronic (1957-67)	19 (73)	2 (7.7)	0 (0)	3 (11.6)	2 (7.7)	26 100 percent

* *From available data for period specified*

gestation was 7.7 months. In our cases there were 3 fetal deaths and one full term viable fetus. Cases not treated had a higher fetal mortality – 8 of 18, as compared to 9 of 34 for all those treated. Maternal mortality during pregnancy and parturition was 14 percent, lower than 29 percent reported before 1943 (22) and 20 percent in 1943-56 (37). Most maternal deaths reported were in the post-partum period (70 percent), but follow-ups are not always available, and one must assume that maternal mortality is really close to 100 percent. At any rate, survival in the puerperium before 1943 was almost nil –only 2 patients lived 2 weeks (22). In 1943-56 this increased to 3.2 months (37). One of our cases has survived 5 months post-partum, but she had been in remission for over 4 years, with a total duration of disease of 66 months thus far.

Table V depicts the different modes of treatment and corresponding fetal and maternal outcomes for 26 cases of chronic granulocytic leukemia in pregnancy for the period 1957-67. Total fetal mortality is 7.6 percent, which is low and similar to that seen

TABLE IV: TREATMENT OF ACUTE LEUKEMIA AND RESULTS (1954-67)

Treatment	No.	Fetal Outcome			Maternal Outcome		
		Died	*V.P.*	*V. T.*	*Death Preg. Part.*	*Death P.P.*	*Living **
No. Treatment	18	8	2	8	2	16	0
Steroid	13	5	2	6	3	9	0
6-MP alone	6	1	1	4	0	3	3
6-MP + steroids	9	1	3	5	1	4	4
6-MP + Methotrexate	4	0	1	3	0	2	1
6-MP + Vincristine	2	2	0	0	1	1	0
Total	52	17	9	26	7	35	8 *
Percent	100	(32.5)	(17.5)	(50)	(14)	(70)	(16)

V.P. - Viable premature, V. T. - Viable term, Preg. & Part. - Pregnancy and parturation (inc. 24 hrs. post partum)
P.P. - Post partum (not including first 24 hours post-partum)

* - *Remission until date of report or no further data available. (2 of 52 cases, percent calculated on basis of 50)*

in 1943-56 by Sheehy (29). There is a slight improvement over fetal mortality before 1943– McGoldrick and Lapp– (22) which was 16 percent. There is no significant difference in fetal mortality between those cases not treated – 1 of 7 versus 1 of 19 in those treated. Of significance is the fact that in 11 cases where busulfan has been the only treatment given all have terminated in viable term deliveries, although 6 of the newborns have weighed less than 2500 g –low birth weight infants (35). Maternal mortality in pregnancy and parturition was 0, as in 1943-56 (29) but slightly improved over that in 1943 (22) of 7 percent. Fifty two percent of mothers were reported as living and doing well at the time of reports, which goes along with the mean survival time of 33.1 months

TABLE V: TREATMENT OF CHRONIC GRANULOCYTIC LEUKEMIA AND RESULTS (1957-67)

Treatment	No.	Fetal Outcome			Maternal Outcome				
		Died	*V.P.*	*V.T.*	*Death*	*P.eg.*	*Part.*	*Death P.P.*	*Living **
No Treatment	7	1	0	6	0			4	3
Busulfan	11	0	0	11 **	0			3	5
Busulfan, X-Ray	4	1	0	3	0			1	3
Bus. 6-MP, X-Ray	2	0	1	1 ***	0			2	0
6-MP, X-Ray	2	0	2	0	0			1	1
Total	26	2	3	21	0			11	12 *
Percent	100	(7.6)	(11.5)	(80.9)	(0)			(47.9)	(52.11)

V.P., V.T., Preg. and Part., P.P. - see Table IV.

** - Remission at time of reports or no additional data available (none on 3/26 cases; percent maternal outcome calculated on basis of 23 cases).*

***. Low birth weight; less than 2500 gm in 6/11 term infants.*

****-Diamond (1960) Multiple congenital anomalies, died 10 weeks age.*

observed by Sheehy (29) in 1958. This survival time is similar to that reported by Tiney (32) for 1,090 patients with chronic granulocytic leukemia in the general population, where median survival was 2.7 years.

The few available reports on follow-up studies of children born to leukemic mothers by Ask-Upmark (1), Bjure (3) and Diamandopolous and Hertig (11) reveal no evidence of long term derangements in these children. To date there are two case reports —Cramblett (8) and Bernard (2)— of acute lymphoblastic leukemia occurring in siblings born to mothers with the same disease at the time of delivery.

The relative rarity of leukemia in pregnancy is related to the rarity of occurrence of leukemia in females of the childbearing age. Thus, in reviewing the U. S. Vital Statistics for 1950 Yahia (37) found an annual death rate for acute leukemia of 2/100,000 females, with 1/100,000 females in the 15-45 age range. Maloney (25) reported that in 1955-63 at the Boston City Hospital of 205 cases of acute and 183 cases of chronic leukemias only 18 females with acute and 12 with chronic leukemia were of the childbearing age. Among these no leukemia was found during pregnancy. Ask-Upmark (1) found that in 1958 in Sweden there were 589 deaths from leukemia and erythremia, of which 247 were females and only 11 in the 15-44 age range. Infertility on the basis of leukemic infiltration of the reproductive tract has been described by Lieta (21). This seems to be a rare occurrence. Multiple pregnancies in the same mother affected with chronic granulocytic leukemia have been noted (1, 14, 15, 24). From the data available, it seems that females of the childbearing age with chronic granulocytic leukemia do not have impaired fertility, whereas those with acute leukemia may become pregnant if they survive long enough and are well controlled, provided of course that the chemotherapeutic agents they receive have no ill-effects on the fertilized ovum.

As for the type of leukemia, Wintrobe (36) points out that the expected proportion for the involved age group would be 40 percent acute and 60 percent chronic leukemias, but in the past 10-year period the relative incidence of the acute leukemias has been higher. Whether this represents a decrease in the reporting of cases of chronic leukemia with pregnancy or on actual higher incidence of pregnancy associated to prolonged survival time in patients with acute leukemia is not known.

The onset of acute leukemias is usually in the second and third trimesters (60 percent in our review). This is of therapeutic significance, since treatment with anti-metabolites in the first trimester is potentially much more harmful to the fetus than during the latter part of gestation. Furthermore, if onset is in the first trimester the chances for maternal survival until term are markedly diminished, in view of the natural history of the disease. In the chronic leukemias the onset is usually prior to gestation, more than one year in over one-half of cases (19, 22). Our review supports this view, since 73 percent of cases had their onset prior to gestation. Obviously the chances for a successful delivery are less if the onset occurs late in the course of the disease, when exacerbations and crises are most common.

Treatment varies with the type of leukemia. Acute leukemia presents a difficult therapeutic problem, since the complications of infection and hemorrhage worsen the prognosis for a successful gestation and delivery. Infections should be detected early and treated with specific antibiotics. Hemorrhagic manifestations may occur and be specially troublesome at the time of delivery, even more so if a Cesarean-section is contemplated due to an obstetrical indication. Most commonly bleeding is related to thrombocytopenia (25), but hypofibrinogenemia may occur (16, 37), specially

in the acute myelocytic leukemia of the promyelocytic variety. In one of our cases this latter diagnosis was made and the patient presented severe bleeding problems, with fibrinogen levels which were low for those encountered in pregnant patients normally and markedly elevated fibrinolysin titers. Fibrinogen, 2-4, with fresh whole blood is the treatment of choice, and Yahia (37) points out that fresh blood offers the advantage of higher titers of fibrinolysin inhibitors over stored bank blood. Regarding the use of steroids and/or antimetabolites there are controversial views on the potential teratogenic effects of these drugs, specially when used in the first trimester, and on their influence on fetal and maternal outcomes. In animal experiments Thiersch (31) and Bragonier (5) have demonstrated teratogenic effects caused by 6-MP, but doses used were usually large and animals vary in sensitivity to drug action and in the period of gestation at which they are most sensitive to toxic effects of drugs (30). Six-mereaptopurine has been shown to cause chromosomal changes in bone marrow cell series of patients with acute leukemia (27). However, in a review by Sokal and Lessman (30) in 1960, and in our review, no congenital anomalies were associated to the use of 6 MP alone. In the first trimester 6-MP has been used alone in one case (16) with a normal fetal outcome, but in 5 cases given 6 MP plus steroids in this period there were 3 fetal deaths (25). In one of our cases, 6-MP plus steroids were given prior to conception and continued throughout pregnancy with a normal term fetus.

Steroids have been associated with fetal anomalies and adrenal hypofunction in the newborn (34). The use of large doses may cause premature births (10). Hoover and Schumaker (20) conclude that they may cause abortion and fetal anomalies, specially when used in the first trimester. However, in small doses steroids may be used without ill effects on the fetus (10, 17). Infants born to patients receiving steroids should be watched closely for the occurrence of adrenal hypofunction.

Methotrexate has been associated to abortion and congenital anomalies (23, 33) and should not be used. Regarding Vincristine, no specific reports are available in the literature, but in our present review it was used on two occasions, both terminating in fetal deaths. Since this may be a reflection of the poorer condition of the patients requiring Vincristine, no conclusions can be reached on this particular drug. X-ray therapy is most dangerous potentially (17) and has been associated with gross developmental defects incompatible with life (26).

In general it may be stated that ideally, in terms of potential fetal effects, no steroids or antimetabolites should be used, but our review shows that fetal and maternal mortality in those cases not treated was higher than in those treated and thus it appears that in the majority of cases the severity of the process may make it necessary to use these drugs. A trial with steroids in small doses (Prednisone 25-50 mg daily) should be attempted, specially during the first trimester, and if no improvement occurs then 6-MP is the antimetabolite of choice in doses of 2.5 mg/kg/day (2). X-ray therapy for local leukemic infiltrates may be used with adequate shielding, but only on those cases where it is indicated. All other antimetabolites, in general, should be avoided, specially methotrexate.

In the chronic leukemias, no treatment may be required in many cases without significant alterations in maternal and fetal outcomes, but if the patient is in an exacerbation, with increasing WBC count and splenomegaly the agent of choice is busulfan (17, 25) in doses of 2-4 mg/day. In 1958 Murphy (26) described gross developmental defects in animals incompatible with life after the use of large doses of busulfan (although to a lesser extent than N-

mustard, TEM, Thiotepa and Chlorambucil), but again Sokal and Lessman (30) found no reports of fetal anomalies in human beings when used alone. Eleven reported cases to date of chronic granulocytic leukemia treated with busulfan alone have terminated in viable term deliveries, although most of the newborns have had a low birth weight (13, 25). Long term follow-up is needed, as Bollag (4) described sterility and atrophic gonads in rat siblings appearing normal at birth after administration of *large* doses of busulfan to mothers. Furthermore, synergistic actions of busulfan when used with other drugs has been suggested by the case reported by Diamond (12) in which a newborn with multiple congenital anomalies who died at the age of 10 weeks was born to a leukemic mother treated with both 6-MP and busulfan in the first trimester. X-ray therapy for massive splenomegaly may be used with adequate shielding, and of course, hemorrhage and sepsis are treated as previously described for acute leukemia.

As regards prognosis, maternal mortality during pregnancy and parturition and fetal mortality in chronic leukemia were always low and have remained almost unchanged by the advent of chemotherapy. In acute leukemia maternal mortality improved from prior to 1943 to 1956 on the basis of blood transfusions, antibiotic therapy and adequate general care, but has improved even more with antimetabolite therapy (20). Fetal survival increased greatly with conservative measures, but has not changed considerably in the last 10 years contrasted to 1943-56. Thus the greatest improvement lies in the increased total maternal survival time which is due largely to the advent of steroid and antimetabolite therapy. Along with this there has been a definite decrease in the incidence of prematurity as compared to the years before 1956 when such therapy was not in use in most cases. One of our cases of acute lymphoblastic leukemia has been in remission for 66 months with 6-MP and steroid therapy, and in the literature there are reports of approximately 70 such "long-term" survivors in acute leukemia (6).

Children born to leukemic mothers seem to have a normal long term survival according to the few reports available in the literature (1, 3, 11) on follow-up of these children. Transmission of leukemia to children by affected mothers remains an interesting hypothesis. Rigby (28) has shown passage of leukemia cells across the placenta and their detection in the peripheral blood of the offspring. Supporters of the viral etiology of leukemias have postulated that the low incidence of leukemia in children born to leukemic mothers may be explained on the basis of host resistance or differences in susceptibility of the fetuses to the leukemic virus (18). To date only 2 cases of acute lympho-blastic leukemia in siblings of mothers with the same disease have occurred (2, 8).

Summary

The coincidence of leukemia and pregnancy is rare and it presents difficult therapeutic problems which require a clear understanding of the problems involved. This can be achieved only through reporting of all cases and review of larger series than those seen by a single worker in the field. Four case reports of acute leukemia in pregnancy are presented and the literature on this subject reviewed. A total of 27 cases of chronic granulocytic and 59 cases of acute leukemia have been reported in the period 1958-1967. As compared to previous years, the relative incidence of acute leukemias has increased, but the incidence, age, race and time of onset have remained the same. Fetal mortality and maternal mortality during pregnancy and parturation in chronic leukemia have not improved significantly after the advent

of steroid and antimetabolitc therapy, whereas in the acute leukemias there has been definite improvement in both, specially in maternal survival during the past 10 years. Therapeutic principles with special consideration to possible effects on the fetus are discussed. Long term survival of children born to leukemic mothers is not apparently altered, but follow-up reports on these children are inadequate.

Resumen

La coincidencia de la leucemia con el embarazo es rara y presenta difíciles problemas terapéuticos. Se presentan cuatro reportes de casos de leucemia aguda en el embarazo y se repasa la literatura sobre este tema. Un total de 27 casos de leucemia crónica granulocítica y 59 casos de leucemia aguda en el embarazo han sido reportados en el período 1958-1967. Comparado con años previos, la incidencia relativa de las leucemias agudas ha aumentado, pero la incidencia absoluta, edad, raza y tiempo al comenzar la enfermedad se han mantenido iguales. La mortalidad fetal y la mortalidad maternal durante el embarazo y el parto en las leucemias crónicas no han mejorado significativamente después de la introducción de la terapia con esteroides y antimetabolitos, mientras que en las leucemias agudas ha habido un progreso definido en ambas, especialmente en la supervivencia maternal durante los últimos 10 años. Se discuten principios terapéuticos, con especiales consideraciones a posibles efectos sobre el feto. La supervivencia a largo término de niños nacidos a madres leucémicas, aparentemente no es afectada, pero los reportes posteriores sistemáticos sobre estos niños son inadecuados.

Acknowledgment

The author is indebted to Dr. Norman Maldonado, Head of the Hematology Section of the University of Puerto Rico School of Medicine for his guidance in the preparation of this manuscript.

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CHORIOCARCINOMA IN PUERTO RICO
A 15-year Study

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Choriocarcinoma is one of the most peculiar and malignant neoplasms arising in the female genital tract. Its unique biologic characteristics have resulted in a degree of interest far out of proportion to its incidence among malignant neoplasms. The successful transplantation of the human choriocarcinoma to the hamster cheeck pouch by Hertz (10) has provided a new tool for studying the natural history of this neoplasm. Wynn's (20) report on electron microscopic studies of transplanted choriocarcinoma has focused attention on the ultra-structure of malignant syncytiotrophoblast.

In spite of these great advancements, a review of the reported cases is still of importance, inasmuch as it may offer some clues to the possible etiological factors and contribute to early detection and diagnosis of this unusual malignant neoplasm.

It is well known, that some characteristics upon which the diagnosis of choriocarcinoma is based cannot be determined until after examination of the intact uterus. Trophoblastic invasion of the uterine wall and of the decidua is seen in both normal pregnancy and with benign hydatidiform mole. The histologic picture thus produced has been very frequently misinterpreted as choriocarcinoma. Such errors are so common that they have greatly influenced the statistics of choriocarcinoma which is not so common as some have indicated, but which is far more malignant that would appear from reports of material which unquestionably included some benign choriomatous lesions (9). For these reasons, the diagnosis of choriocarcinoma must be firmly established in each patient to make the data meaningful (1).

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Presented in part at the Annual Meeting of the Section of Obstetrics and Gynecology of the Puerto Rico Medical Association, March 1967, San Juan, Puerto Rico.

Material and Methods

The data presented in this study was obtained from the records of 44 cases of choriocarcinoma reported to the Central Cancer Registry of the Division of Cancer Control of the Department of Health. These cases were diagnosed in different hospitals of Puerto Rico from 1950 to 1965.

Additional information, not found in the Cancer Registry records, was obtained by reviewing the clinical record of each patient in the institution or hospital which reported the case to the Central Cancer Registry and through personal or written communication with the patients or nearest relatives.

In 29 patients, the diagnosis was made after hysterectomy and examination of the intact uterus (20 patients), after autopsy and examination of the internal genitalia (7 patients) or from biopsy of metastatic lesions (2 patients). In these two patients, positive pregnancy test and persistently elevated chorionic gonadotrophins supported the diagnosis.

In 13 patients, the diagnosis of choriocarcinoma was made after microscopic examination of material obtained by dilatation and curettage. In 12

of these patients, the diagnosis was confirmed after examination of the intact uterus. Persistently elevated serial titers of chorionic gonadotrophins in the urine and post-mortem examination of the uterus, confirmed the diagnosis in the other patient.

Two of the 44 cases reported to the Cancer Registry were not included in this study. In one case we could not determine how the histologic diagnosis was made. In the other case, the diagnosis of choriocarcinoma was made after microscopic examination of material obtained by curettage, however pregnancy tests and subsequent curettages were reported as negative. This patient received no further treatment and was asymptomatic two years later. Additional follow up was not available. Even though this case could have been a choriocarcinoma, we could not get objective evidence to support the diagnosis.

Results

Of the 42 confirmed cases of choriocarcinoma reported to the Cancer Registry, 41 were women. There was one male patient (Table I). Among these 41 cases, 39 developed from trophoblastic tissue within the uterine cavity; another followed an ectopic pregnancy in a fallopian tube. The remaining case arose from a teratoma of the left ovary. The condition arose from a teratoma of the left testicle in the male patient.

The data that follows concerns the 40 female patients in which the malignancy was definitely related to the preceding pregnancy.

TABLE I: HISTOLOGIC DIAGNOSIS AND PRIMARY SITE OF CHORIOCARCINOMA

Histology	Primary Site	No.
Choriocarcinoma	Uterus	39
Choriocarcinoma	Fallopian Tube	1
Malignant germ cell tumor and choriocarcinoma of left ovary	Ovary	1
Embryonal carcinoma and choriocarcinoma of left testicle	Testicle	1

Year Distribution:

Cases of choriocarcinoma were evenly distributed among the years of the period. The ratio of total cases to the total number of births was 1:32,460 (Table II).

Age Distribution:

The youngest patient reported was 16 years old. The oldest was 50 years old. The average age of patients in this series was 31 years (Table III, Fig. 1).

TABLE II: INCIDENCE OF CHORIOCARCINOMA IN PUERTO RICO (21)

Year	No.	Deliveries
1950	3	89,452
1951	4	87,903
1952	5	83,690
1953	2	80,649
1954	4	81,127
1955	2	82,267
1956	-	81,229
1957	4	78,985
1958	1	78,662
1959	2	77,340
1960	2	78,291
1961	2	77,765
1962	1	78,864
1963	-	79,568
1964	4	80,969
1965	4	81,658
1950-65	40	1,298,419 *

** - Ratio: 1:32,460*

TABLE III: AGE DISTRIBUTION OF CHORIOCARCINOMA IN ASIA, TAIWAN, UNITED STATES AND PUERTO RICO

Age	Asia (13)		Taiwan (12)		U. S. (13)		Puerto Rico	
	Cases	*Percent*	*Cases*	*Percent*	*Cases*	*Percent*	*Cases*	*Percent*
19	5	3.6	1	4.5	6	16.6	6	15.0
20-29	54	38.6	5	22.8	17	47.2	16	40.0
30-39	50	35.7	8	36.3	11	30.6	6	15.0
40-49	23	16.4	5	22.8	2	5.6	11	27.5
50-59	6	4.3	3	13.6	-	-	1	2.5
Unknown	2	1.4	-	-	-	-	-	-
Totals	140	100	22	100	36	100	40	100
Av. Age	33		36		28		31	

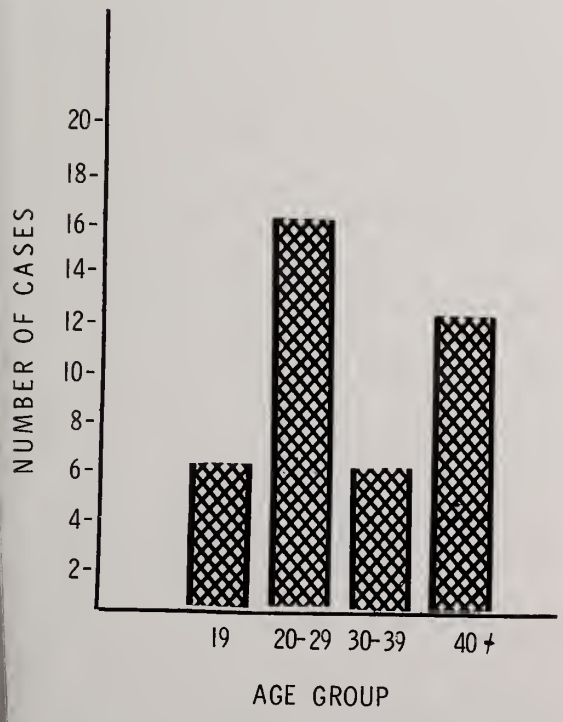


Fig. 1: Age distribution of choriocarcinoma, Puerto Rico 1950-1965.

Type of Pregnancy Preceding Choriocarcinoma:

The frequency of the type of pregnancy preceding choriocarcinoma varies from country to country. In our series, 45 percent of the cases were preceded by a mole, 25 percent by an abortion and only 15 percent by a full term pregnancy (Table IV).

Interval Between Pregnancy and Diagnosis:

The time intervals between the end of the preceding pregnancy and diagnosis of choriocarcinoma were all within 3 years (Table V). Twenty-eight cases (70 percent) were diagnosed within twelve months after the end of the preceding pregnancy. There were two cases in which the diagnosis was made twenty-four to thirty-six months after. These followed an abortion and a molar pregnancy.

Gravity:

Thirty patients (75 percent) were multi-

TABLE IV: TYPE OF PREGNANCY PRECEDING CHORIOCARCINOMA (12)

Country	Hydatidiform Mole	Abortion	Full Term	Tubal	Unknown
U. S.	40-50	25-40	20-22	2.5	-
Canada	40	33	25	-	-
Indonesia	70	14		7.4	-
Philippines	63	18	4	-	-
Japan	67	25	-	6.3	-
Taiwan	50-81	9-19	4-15	4.7	-
Puerto Rico	45	25	15	2.5	12.5

gravidas. There were 3 primigravidas among our patients. This data could not be obtained in 7 of the cases reported (Table VI).

TABLE V: INTERVAL BETWEEN PREGNANCY AND DIAGNOSIS

Time Interval	Number
1 mo.	4
1 - 2 mo.	6
2 - 3 mo.	4
3 - 4 mo.	7
4 - 5 mo.	2
5 - 6 mo.	3
6 - 12 mo.	2
12 - 24 mo.	-
24 mo.	2
Unknown	10
Total	40

TABLE VI: GRAVITY OF PATIENTS WITH CHORIOCARCINOMA

Gravity	1	2	3	4	5	6	7+	Unknown	Total
No.	3	9	5	3	4	2	7	7	40

Initial Symptomatology:

In twenty-nine patients (72.5 percent), vaginal bleeding was the initial symptom. The other patients presented varying symptomatology (Table VII).

Stage of the Disease at Diagnosis:

A metastatic lesion was said to exist if it could be demonstrated by microscopic examination of biopsy material, by roentgen examination, by exploration of abdominal viscera at the time of hysterectomy or after examination of autopsied material. Since some of these methods often fail to demonstrate a lesion in an inaccessible organ, it is probable that metastases were present in some other patients, but could not be detected.

In nineteen patients (47.5 percent) the malignancy was localized within the uterine cavity at the time of diagnosis (Table VIII). Two of this group subsequently developed distant metastases after hysterectomy. Two patients with regional metastases at the time of diagnosis subsequently developed distant metastases after major operative procedures (bilateral oophorectomy in one case; hysterectomy in the other).

Twenty-three patients (57.5 percent) developed regional or distant metastases either before the diagnosis was made or subsequent to a surgical procedure. Fifteen patients (37.5 percent) had metastases to the lung. Eight patients (19 percent) had metastases to the vagina and two patients (5 percent) had metastases to the brain (Table IX). Some patients in our series had multiple metastases.

Ten patients (67 percent) with metastatic lesions in the lung were twenty-nine years of age or younger, while only 5 patients (33 percent) were thirty years or older (Table X). Of twenty-two patients 29 years of age or younger, 45.4 percent had metastases to the lung, while only 27.8 percent of eighteen pa-

TABLE VII: INITIAL SYMPTOMATOLOGY IN CHORIOCARCINOMA

Symptom	No.
Vaginal bleeding	29
RLQ pain and hematuria	1
RLQ pain	1
Suprapubic pain	1
Cough	1
Paresthesias in sacral region	1
Unknown	6
Total	40

TABLE VIII: STAGE AT TIME OF DIAGNOSIS

Stage	No.	Percent
Localized *	19	47.5
Regional Metastases	8	20.0
Distant Metastases	8	20.0
Regional and distant	5	12.5
Total	40	100

**. Two of the patients with the disease localized within the uterine cavity at the time of diagnosis subsequently developed distant metastases after surgical procedures.*

TABLE IX: SITES OF METASTASES

Site	Number
Lung	15
Vagina	8
Liver	3
Peritoneum	3
Parametrium	2
Bladder	2
Brain	2
Infundibulo-pelvic ligament	1
Broad ligament	1
Abdominal wall	1
Lumbosacral spines	1
Pelvic wall	1
Cervix	1
Adrenal gland	1
Regional lymph nodes	1
None	19

TABLE X: METASTATIC LESIONS TO THE LUNG BY AGE OF PATIENT

Age Group	No.	Metastases to Lung
19	6	4
20-29	16	6
30-39	6	1
40-49	11	4
50-59	1	-
60	-	-
Total	40	15

tients 30 years or older had similar lesions.

Lutein Cyst:

Ovarian lutein cysts were present in seventeen patients (42.5 percent). Eleven of these patients were 29 years of age or younger (Table XI).

TABLE XI: FREQUENCY OF OVARIAN LUTEIN CYSTS

	Number
Cysts present	17
Not present	13
Not determined	10
Total	40

Treatment:

At the present time chemotherapy is considered to be the treatment of choice for metastatic trophoblastic tumors. All other forms of treatment must be considered adjunctive to the use of chemotherapy. These include: hysterectomy, oophorectomy, radiation, hormonal and inmunologic treatment.

Abdominal hysterectomy with or without oophorectomy was the initial treatment given to twenty-eight of the forty patients reported (Table XII). Eight of these patients received radiation therapy, nitrogen mustard, stilbestrol or a combination of these agents in addition to hysterectomy. Since it is generally accepted (1) that such additional therapy did not significantly alter the results, these patients were included together with those in which hysterectomy was the only treatment given.

Methotrexate was used in 8 patients, all of whom had metastatic lesions at the time of diagnosis except one patient in whom metastases developed after hysterectomy. This latter patient as well as three others in the group had had hysterectomies before chemotherapy was started (Table XII).

Follow Up and Survival:

Fifteen of twenty-eight patients treated by hysterectomy are living and well over five years after diagnosis (Table XIII). Eleven of these patients had the malignancy localized in the uterine cavity at the time of diagnosis. The other four patients had metastatic lesions. In addition to hysterectomy, three of these four patients received radiotherapy (one also received nitrogen mustard). The fourth patient had an excission biopsy of metastases to the vagina.

Of the seven dead patients in which hysterectomy was the main treatment, five had metastases at the time of operation and one developed metastatic lesions after the procedure. Of the eight patients that received methotrexate, four died within twelve months after diagnosis (Table XIII).

Of the fifteen patients who died, thirteen had metastatic lesions at the time of diagnosis. In another patient, metastases developed after hysterectomy. In this group of patients, recurrences were reported in two cases after remissions of eight and twenty-four months respectively.

Of the 16 patients living and well after five years, eleven had the malignancy localized within the uterine cavity at the time of diagnosis (Table XIV). Hysterectomy was the only treatment given to these eleven patients. Four patients had regional metastases at the time of diagnosis and received further adjunctive therapy in addition to hysterectomy. One patient had distant metastases at the time of diagnosis and received methotrexate in addition to hysterectomy. No recurrences have been reported in this group of 16 patients.

In support of the concept that most of the deaths in patients with choriocarcinoma occur within the first year, we noted that 93.4

percent of the fatalities in our series occurred within twelve months after diagnosis, being evenly distributed throughout the twelve months period (Table XV).

Discussion

During a fifteen-year period (1950-1965) 42 well documented cases of choriocarcinoma were reported to the Central Cancer Registry of Puerto Rico. This series represent the total number of cases diagnosed in Puerto Rico during the stated period of time. In addition to the legal requirements for reporting cancer cases, the Registry systematically searches for unreported malignancies, including an annual check of all pathologists' registries, admission books and diagnosis index of each medical record room in all hospitals throughout the island.

For the purpose of comparison, our data represents the whole country incidence. Data from other countries, often shows frequencies obtained from one or a limited number of hospitals in a particular geographical area.

TABLE XII: TREATMENT

Therapy	Stage at Time of Diagnosis					
	Loc.	*Reg.*	*Dist.*	*Reg. & Dist.*	*Unk*	*Total*
Hysterectomy	18	7	1	2	-	28
Hysterectomy * & methotrexate	-	-	2	1	-	3
Hysterectomy, methotrexate & velban	1	-	-	-	-	1
Methotrexate	-	-	1	1	-	2
Methotrexate & actinomycin D	-	-	1	-	-	1
Methotrexate, ** actinomycin D & velban	-	1	-	-	-	1
X-ray	-	-	1	-	-	1
None	-	-	2	1	-	3
Unknown	-	-	-	-	-	-
Total	19	8	8	5	-	40

** - In one patient a remission of eight months was obtained.*
*** - Bilateral oophorectomy performed before chemotherapy.*

TABLE XIII: SURVIVAL AND TYPE OF TREATMENT

Results	Type of Treatment									
	Hysterectomy	*Hysterect. & Metho.*	*Hysterect. Metho. & Velban*	*Methotrexate*	*Metho. & Actino D*	*Metho. Actino D & Velban*	*X-ray*	*None*	*Unk.*	*Total*
Liv. & well over 5 years	15	1	-	-	-	-	-	-	-	16
Liv. & well 4-5 years	-	-	-	-	-	-	-	-	-	-
Liv. & well 3-4 years	1	-	-	-	-	-	-	-	-	1
Liv. & well 2-3 years	-	-	1	-	-	-	-	-	-	1
Liv. & well 1-2 years	2	1	-	-	-	1	-	-	-	4
Liv. & well up to 1 yr.	-	-	-	-	-	-	-	-	-	-
Died 1-12 mo. after Dx.	6	1	-	2	1	-	1	3	-	14
Died 28 mo. after Dx.	1	-	-	-	-	-	-	-	-	1
Lost Cases	3	-	-	-	-	-	-	-	-	3
Total	28	3	1	2	1	1	1	3	-	40

TABLE XIV: SURVIVAL AND STAGE OF THE DISEASE AT DIAGNOSIS

Result	Stage					
	Loc.	*Reg.*	*Dist.*	*Reg. & Dist.*	*Unk.*	*Total*
Liv. & well over 5 years	11	4	1	-	-	16
Liv. & well 4-5 years	-	-	-	-	-	-
Liv. & well 3-4 years	1	-	-	-	-	1
Liv. & well 2-3 years	1	-	-	-	-	1
Liv. & well 1-2 years	2	1	1	-	-	4
Liv. & well up to 1 year	-	-	-	-	-	-
Died 1-12 mo. after Dx.	2	1	6	5	-	14
Died 28 mo. after Dx.	-	1	-	-	-	1
Lost during 1st yeat after Dx	2	1	-	-	-	3
Totals	19	8	8	5	1	40

TABLE XV: TIME BETWEEN DIAGNOSIS AND DEATH

Time (Months)	Number
1	3
1-2	3
2-3	2
3-4	-
4-5	2
5-12	4
12	1
Total	15

Among the 42 cases, there were 41 female patients and one male in whom the malignancy developed from a teratoma of the left testicle. Twenty-six possible cases of choriocarcinoma in males arising from teratomas had been reported in the literature up to 1956 (9). Seventeen of these were thought to be primary in the abdomen, seven in the thorax and two in the region of the pineal gland.

In forty female Puerto Rican patients the malignancy developed from embryonic trophoblast either within the uterine cavity (39 cases) or within the Fallopian tube (1 case). In the other female patients, the malignancy arose from a teratoma of the left ovary.

Primary choriocarcinoma of the ovary may be regarded as gestational or non-gestational. The gestational type would be presumed to have followed an ovarian pregnancy, provided that metastases from a primary uterine choriocarcinoma could be ruled out. The non-gestational type arises from a teratoma or embryonal rest. Fourteen cases of teratomatous ovarian choriocarcinoma had been reported up to 1956 (9); eleven cases occurred in patients less than fourteen years of age.

Grisbisic (7), in an excellent review of the literature up to 1956 was able to obtain only sixty cases of extrauterine choriocarcinoma. Bobrow and Bell (4), in their study of 905 cases of ectopic pregnancy, reported that none of these cases terminated in benign or malignant trophoblastic disease.

Primary choriocarcinoma of the Fallopian tube may originate either from an ectopic pregnancy, an intrauterine pregnancy that has spread to the tube (via embolic transport of chorionic villi to the tube) or from teratogenous change within the tube (9). An unusual characteristic of choriocarcinoma of the Fallopian tube following ectopic pregnancy is that it almost never is preceded by hydatidiform mole (16).

The incidence of choriocarcinoma in Puerto Rico appears to be higher than in the United States but significantly lower than in Asian countries (12, 13). The approximate incidence zin the United States is 1:70,000 deliveries (2). Data obtained from studies of choriocarcinoma in Asia revealed a ratio of 1:250 to 1:3,708 deliveries (6).

The average age of patients with choriocarcinoma in Puerto Rico was 31 years compared with 28 years in 36 patients reported from the United States (13). The average age of the 140 and 22 patients reported from Asia and Taiwan was 33 and 36 years respectively (12, 13). Chien (12) stated that the difference in the average age of patients with malignant trophoblastic disease in the United States and Taiwan could not be explained by the difference in the age and parity distribution of births between these two countries.

There were two cases of choriocarcinoma which followed an abortion and a molar pregnancy, in which the diagnosis was made 24 to 36 months after the end of the preceding pregnancy. Because of this, abortion and specially molar pregnancies should be carefully followed-up for two to three years. It should be recalled that in our series, choriocarcinoma was preceded in 45 percent of the cases by

increases to 50-80 percent (Table VI).

Seventy percent of our cases were diagnosed within 12 months after the end of the preceding pregnancy. In 26 cases from Taiwan reported by Wei (15), all cases were diagnosed within three years after the preceding pregnancy but only 50 percent within one year.

In comparison to the total number of deliveries in each age group, the incidence of choriocarcinoma in Puerto Rico is disproportionately higher in the age group of over forty (Table XVI, Fig. 2). The incidence of choriocarcinoma in this age group is much higher than the frequency in a similar age group in the United States (Table XVII), but approximates the frequency in a similar age group reported from Taiwan (12, 13, 15).

The above findings would imply that in Puerto Rico, multigravidas forty years or older should receive special pre-natal care and postpartum follow-up, especially in the event of an abortion or a molar pregnancy, since this seems to be the higher risk age group.

Vaginal bleeding was the most common initial symptom in our cases even in the presence of regional or distant metastases.

Metastases to the brain were rare as compared to those reported in other series (12, 15). Wei (15) reported that in 96.1 percent of his cases, vaginal bleeding was the most prominent symptom. Metastases to the lung (84.5 percent), vagina (50 percent) and brain (42.2 percent) were the common clinical features in his series.

Hsu (12) in his report of 27 cases from Taiwan, found that 54.5 percent, 31.8 percent and 31.8 percent of his series had metastases to the lung, vagina and brain respectively. The lung was also the most common site of metastases in our series and these lesions appeared to be more common in the younger age group. Metastatic lesions in our patients appear to develop relatively early in

TABLE XVI: BIRTHS AND CHORIOCARCINOMA BY AGE OF MOTHER IN PUERTO RICO (1950-65) (21)

Age Group	No. of Births	Cases of Choriocarcinoma	Ratio
19	183,931	6	1:30,655
20-29	680,430	16	1:42,526
30-39	288,793	6	1:48,132
40+	45,436	12	1: 3,786
Unknown	55,047	-	-
Stillbirth	44,782	Not. Spec.	-
Total	1,298,419	40	1:32,460

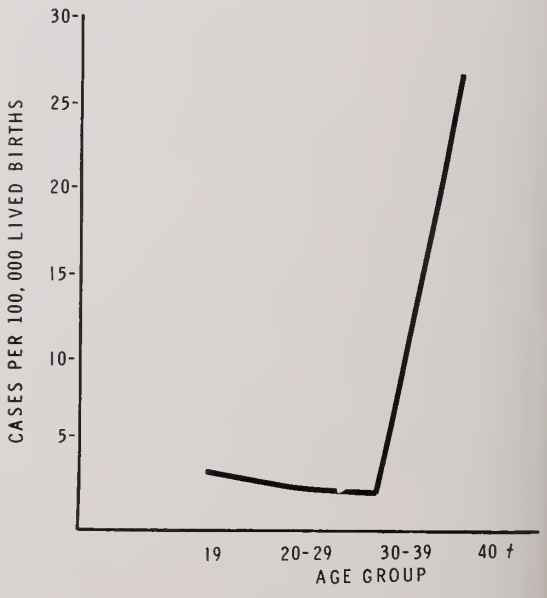


Fig. 2: Risk of developing choriocarcinoma, Puerto Rico 1950-1965.

TABLE XVII: BIRTHS* AND CHORIOCARCINOMA BY AGE OF MOTHER IN THE UNITED STATES (36 CASES) *****

Age	No. of Births	Cases of Choriocarcinoma	Ratio
19	485,152	6	1:80,858
20-29	2,347,108	17	1:138,065
30-39	1,008,744	11	1:91,704
40	88,664	2	1:44,332
Unknown	4,428	-	-
Total	3,934,096	36	1:109,280

**- For age distribution, average of total live births by the age of mother recorded in Demographic Year Book 1949-1958 and 1960 was used.*

***- The thirty-six cases of Choriocarcinoma in the United States was cited from Dr. Iverson's paper (13).*

****- The data that appears in this table was cited from Chien's paper (12).*

the course of the disease.

Eleven of the seventeen patients with ovarian lutein cysts were 29 years of age or younger. This agrees with findings of Brews (3) who states that the development of large cysts is more common in the younger age groups.

The effect of prior hysterectomy upon the result of chemotherapeutic agents could not be evaluated because of the relatively small number of patients in this series. Hertz (11) in his large series reported no difference in the response to chemotherapy between those patients with hysterectomy and those without one, however Spellacy (19) in an excellent review of the literature found six well documented cases of normal pregnancies following the use of methotrexate in the treatment of malignant trophoblastic diseases and added one of his own in which a patient had three successful pregnancies following the use of methotrexate in the treatment of choriocarcinoma. Unilateral or bilateral oophorectomy was performed in most of the patients who had hysterectomies. Stearns (18) and Smalbraak (19) recommended preservation of the ovaries while Hertz (11) reported substantially more favorable result if oophorectomy is performed.

There were 4 patients in our series who developed metastatic lesions after major operative procedures. Brewer (1) in his series of 122 patients from the Albert Mathiew Chorionepithelioma Registry reports that of 70 percent who did not have demostrable metastases at the time of hysterectomy, 40 developed metastatic lesions subsequent to the procedure.

The effect of metastatic lesions on the prognosis is illustrated by the fact that in our series eleven of sixteen patients living and well for over five years had the malignancy localized at the time of diagnosis. Of the fifteen patients who died, fourteen had developed regional or distant metastases, and of twenty-one patients with metastases at the time of diagnosis, fourteen subsequently died.

Brewer's (1) report of absolute five year survival rates of 122 patients with choriocarcinoma treated by hysterectomy showed that of 39 patients living and well for over five years 29 had the malignancy localized at the time of hysterectomy. Of 74 patients who died, all had developed metastatic lesions either before or after hysterectomy. Of 52 patients with metastases at the time of hysterectomy, 40 died within 18 months after the operation.

Most of the deaths in our series occurred within one year after diagnosis. This finding agrees with the observation of Brewer (1) who states that 72 of the 74 deaths in his report of 122 cases occurred within 24 months after

hysterectomy. Wei (15) reports that of his 26 cases, 24 had died within 24 months after diagnosis, 22 within 12 months and 17 within 6 months

Summary

From 1950 to 1965, 44 cases of choriocarcinoma were reported to the Central Cancer Registry of Puerto Rico. Among 42 cases adequately confirmed and supported by objective evidence, there were 40 cases in which the malignancy was definitely related to the preceding pregnancy. The average age in our series was 31 years. Forty-five percent of the malignancies were preceded by a hydatidiform mole.

Seventy-five percent of the patients were multigravidas. Most of them presented vaginal bleeding as the initial symptom usually within 12 months after the end of the preceding pregnancy. Twenty-three patients (57.5 percent) developed regional or distant metastasis either before the diagnosis was made or subsequent to a surgical procedure. The lung was the most common site of metastases and these lesions appeared to be more frequent in the younger age group.

Of the 40 patients studied, 16 are living and well over 5 years after diagnosis. Eleven of these patients had the malignancy localized within the uterine cavity at the time of diagnosis. Fourteen of the deaths occurred within one year after diagnosis. Thirteen of these patients had developed metastatic lesions.

The higher incidence of choriocarcinoma in patients 40 years of age or older is demonstrated. Special pre-natal care and post-partum follow up is recommended for this high risk group of paticnts.

Resumen

En un período de 15 años (1950-1965) se informaron 44 casos de coriocarcinoma al Registro Central del Cáncer en Puerto Rico. De 42 casos confirmados histológicamente, 40 estaban relacionados a un previo embarazo. La edad promedio de los pacientes fue de 31 años. Cuarenta y cinco por ciento (45 porciento) de los casos, fueron precedidos por molas hydatidiformes. Setenta y cinco porciento de los pacientes eran multigrávidas. La mayoría presentó sangría vaginal como síntoma inicial usualmente en un período de 12 meses después del embarazo. Veinte y tres pacientes desarrollaron lesiones metastáticas. Estas se encontraron mas frecuentemente en el pulmón y en el grupo de pacientes menor de 30 años.

De los 40 pacientes estudiados, 16 han sobrevivido por más de 5 años. Once de éstos, tenían el cáncer localizado en la cavidad uterina. Catorce de las muertes ocurrieron en un período de 1 año después del diagnóstico. Trece de estos pacientes habían desarrollado lesiones metastáticas.

La incidencia más alta de coriocarcinoma se encontró en mujeres mayores de 40. Se recomienda especial cuidado pre-natal y frecuentes exámenes post-parto a este grupo de pacientes de alto riesgo.

Acknowledgment

We wish to express our sincere gratitude to the faculty members of the Department of Obstetrics and Gynecology of the University District Hospital and to those private Physicians and Medical Record Librarians who contributed with information and sincere cooperation in the preparation of this paper. We thank Dr. Louis G. Keith for the comprehensive review of this paper.

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PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

Rafael V. Urrutia, Jr.

Primary carcinoma of the Fallopian tube is an extremely rare gynecologic condition. Very few gynecologists will ever encounter one such case during their lifetime practice. It is believed that Raynaud reported the first case of primary carcinoma of the tube in 1847 (1). The first pathological description was given by Rokitanski in 1861; Orthmann in 1886 reviewed 13 cases in the literature prior to that time.

Incidence

Primary carcinoma of the tube is 10 times less common than the secondary metastatic type (1). Reports of incidence have varied from 0.1 percent to 1.6 percent (2, 3). Frankel (3) explains this 1.6 percent on the basis of the low incidence of carcinoma of the cervix in his series due to the fact that most patients at the reporting institution (Beth Israel Hosp., New York City) are predominantly of the Jewish race.

Table I shows a comparison of the relative incidence of the carcinomas of the female genital tract (2).

The next Table (Table II) will show a composite of the incidence in various reported series. Up to 1966, approximately 700 cases have been reported in the English literature.

Hu believes that the true incidence is higher than the reported values, yet many of the cases of tubal carcinoma involve the ovary and may be reported as primary ovarian in origin (4). Tumors involving the tube and ovary were classified as tubo-ovarian tumors and most of these were not included in most series due to the difficulty in ascertaining the true origin.

Etiologic Factors

Hertig believes that the low frequency of tubal carcinoma could be related to the relative stability of the tubal epithelium during the menstrual cycle (9). On the other hand, pelvic tuberculosis and pelvic inflammatory disease (PID) have been blamed on the past

TABLE I: CARCINOMAS OF THE FEMALE GENITAL TRACT

Site	No.	Percent
Cervix	2052	64.0
Endometrium	596	18.7
Ovary	310	9.7
Vulva	170	5.3
Vagina	70	2.2
Fallopian tube	2	.1
Totals	3200	100.0

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as being closely associated etiologic agents to tubal carcinoma. Embryonic rests of Mullerian origin have at some time or another been associated to primary adenocarcinoma of the tube. It has been proven later, that these rests give rise early in life to malginant mixed Mullerian tumors which usually have multiple tissue components. This tumor in the tube is equivalent to sarcoma botryoides of the vagina (10).

The association between PID, tuberculosis and carcinoma is not well established because the first conditions are fairly common and carcinoma is very rare. Sedlis (11) found a 3 percent incidence of tuberculosis in a large series of 232 patients with primary carcinoma of the tube. This value has been corroborated by others (12). (The general incidence of pelvic tuberculosis in general population is 0.4-2 percent) (11). Due to the closeness of these values, it is very doubtful that tuberculosis has any major role as etiologic agent. In spite of this, the histological changes produced by tuberculosis may become strikingly similar to those of carcinoma to the extent of making the differential diagnosis quite difficult at times due to the adenomatoid hyperplasia that follows tuberculous salpingitis (5, 11, 13). Fullerton (5) once postulated that tuberculosis may stimulate the formation of benign papillomas which may later become malignant. It has also been said that benign adenomatous tumors may have a pre-malignant potential (14). Mitchell also postulated that these benign papillomas could become malignant under the effects of gestation (1). Nothing has been shown about this since.

PID is a fairly frequent gynecological condition. Reports have shown a very high incidence of nulliparity associated with tubal carcinoma (11, 12).

The high incidence of PID, association of

TABLE II: INCIDENCE OF CARCINOMA OF FALLOPIAN TUBE

Author(s)	Institution	Years	Gynecological Admissions	Malignancies	Cases	Percent
Hu, Taynor, Hertig (4)	Free Hospital	45	90,611	3,878	12	.31
Fullerton (5)	Cleveland	13	22,330	-	4	-
Mitchell, Mohler (1)	Philadelphia	47	(6,747 salpingectomics)	-	1	-
Emge (6)	Stanford	10	-	1,350	5	.49
Frankel (3)	Beth Israel	10	-	435	7	1.6
	Harlem Hosp.	10	-	687	3	.43
Hayden (7)	Chicago Lying-In	26	-	1,087	12	1.10
Green (2)	Pondville Ca. Hospital	34	-	3,200	2	.10
Dougherty (8)	Charity Hosp. New Orleans	26	-	-	25	-

infertility (both with PID and carcinoma) would support the thesis of PID as a predisposing factor to carcinoma. Anyhow, nowadays most authors believe, that the inflammatory changes seen in the tubes are secondary to the carcinoma (6, 9, 11, 12).

In some of the cases of tubal carcinoma, autopsy has revealed other concommitant diseases in pelvic organs such as endometriotic ovarian cysts, adenomyosis, ovarian papilloma and uterine myomas. Up to now, there seems to be no associated relationship between the malignancy and the other conditions.

Age

Carcinoma of the fallopian tube has a higher frequency in the fifth and sixth decade. The mean age (50-52) is usually less than that stated for carcinoma of the vulva, more than for carcinoma of the cervix and at about the same age for endometrial carcinoma. The youngest patients reported are 18 years old (8, 15) and the oldest 80 years (5, 15). In a series of 232 cases, Sedlis found the distribution shown in Table III.

TABLE III: AGE DISTRIBUTION OF 232 CASES OF CA. OF FALLOPIAN TUBE (11)

Age	Number	Percent
20-29	5	2.2
30-39	10	4.4
40-49	63	27.2
50-59	52	22.2
60-69	29	12.4
70+	10	4.4
Undetermined	63	27.2
Total	232	100.0

Parity and Menstrual Status

A history of sterility has been reported to be a frequent feature in the background of women in whom tubal carcinoma develops. Though figures as low as 27 percent have been reported (4), the average accepted figure for nulliparity in most series stand at about 50 percent (7, 8, 11, 12). About 50 percent or more of the patients are post menopausal (7, 12). Hanton (12) showed that the menstrual status showed no relationship to the grade or type of tumor nor with the survival of the patients.

Symptoms and Physical Features

As is so unfortunately also true of ovarian cancer, carcinoma of the tube is often in a fairly advanced stage before symptoms to bring the patient to her physician appear. Nor is the routine yearly pelvic examination likely to improve the situation significantly, inasmuch as the early asymptomatic tumor that is still confined to the tubal lumen and for which prompt resection may offer hope of cure is frequently not palpable, or equivocal abnormalities may be ascribed to old pelvic inflammatory disease or fibroids. These two lesions frequently coexist with tubal carcinoma and confuse the picture. Furthermore, when symptoms and signs do accompany the early stage of the disease, they are often vague and intermittent. It is therefore important that the physician view with a high degree of suspicion vague pelvic and lower abdominal complaints in women in the fifth and sixth decades of life, particularly when accompanied by abnormal vaginal bleeding or discharge, if tubal carcinoma is to be recognized at a time when resection for cure is still feasible.

Even in the face of definite symptoms and obvious palpable disease in the pelvis, the correct pre-operative diagnosis has only rarely

TABLE IV: SYMPTOMS

Symptoms	No. of Patients		Percent
Metrorrhagia or bloody discharge	119	(28)*	51
Pain or pressure	111	(12)*	48
Leukorrhea	71	(4)*	30.5
Abdominal mass	22	(4)*	9.5
Pain and metrorrhagia	41	(21)*	17.5
Leukorrhea and metrorrhagia	36	(20)*	15.5
Pain, leukorrhea and metrorrhagia	14	(13)*	6.1
None or irrelevant	9		3.8

** - Refers to symptom as being sole presenting complaint.*

been made (4, 13). In spite the difficulty in diagnosis, certain symptoms and findings have been observed with sufficient frequency in association with tubal carcinoma to warrant considering this diagnosis in their presence.

If there be a pathognomonic symptom of tubal carcinoma, it is the intermittent occurrence of a profuse, watery, clear yellow or bloody vaginal discharge which is characteristically abrupt in onset and accompanied by colicky pain, ceases equally rapidly and may recur days or even months later. This is the so called *syndrome of hydrops tubae profluens*, first described by Latzkoi in 1915 (7). This results from the intermittent discharge of secretions and tumor debris from a partially obstructed and distended tube. Unfortunately this syndrome seldom occurs and most series do not report its occurrence (1, 3, 12). In a series of 232 cases, Sedlis reported an incidence of only 4.3 percent. In smaller series it has been reported as high as 8.3 percent (4). Moreover, this syndrome is more frequent with hydrosalphinx associated with other etiological factors (13).

Most authors agree that vaginal discharge, being bloody, serosanguinolent, creamy or watery, is the most common presenting symptom (3, 4, 11). Kneale (13) believes that a yellowish discharge is the most specific of all types and that this is due to products of tubal secretion mixed with autolysis of tumor cellular debris.

Sedlis charted the symptoms of his series as shown in Table IV (11).

Metrorrhagia, the most prominent presenting symptom is usually described as being intermenstrual, post-menopausal (in about 50 percent of patients), vaginal spotting or bloody discharge. Though the most common symptom, it usually occurs late in the disease. This may be due to further narrowing of the uterotubal junction and blood won't be discharged until after accumulating in sufficient quantity in the tube (11).

Pain is the second most common symptom. Though being described in various manners (colicky, dull, crampy or pulling sensation), the colicky-crampy type seems to be the most common. This is due to distention of the tube and irritation of the musculature therefore increasing the peristaltic activity in an

attempt to get rid of contents (2, 11). Distention alone may lead to the dull type of pain. Characteristically, the pain was usually unilateral and on the side of the lesion (3, 4). The pain occurs earlier than in carcinoma of the ovary and endometrium (1).

In so far as the physical evaluation, approximately two thirds of all patients with tubal carcinoma had a palpable pelvic mass (adnexal?) at the time of initial visit to her physician (11, 12).

A classic triad of pain, palpable mass and vaginal discharge has been described as being descriptive of tubal carcinoma, but unfortunately too, this occurs only in approximately 11 percent of all patients (12).

Pathologic Features

The distal two thirds of the tube is the site most commonly involved by carcinoma (9, 13). The gross appearance of the tumor is extremely variable. Size usually fluctuates from 1 - 17 cm; it may look purple, gray or yellow and may seem or feel doughy, firm, granular, friable or of a cheese-like consistency. Usually the ostium is closed (partially or totally) which helps prevent spillage of malignant cells into the peritoneal cavity.

The incidence of bilateral lesions is stated in the literature as being close to 30 percent (6, 11). Sedlis (11) believes that the bilateral involvement appears to be a manifestation of multicentric origins rather than of metastasis. This is supported by frequent occurrence of bilateral involvement in the absence of metastasis, the symmetrical development of lesions (in so far as size), the demonstration of various stages of development of the carcinoma from normal epithelium on both sides, and the usual absence of uterine implantations expected to occur if extension takes place by direct extension from the opposite tube through the uterine cornu.

Several criteria must be fulfilled before the diagnosis of primary carcinoma of the tube is made (4). These are: (a) grossly the main tumor is in the tube; (b) microscopically, chiefly the mucosa should be involved and should show a papillary pattern; (c) if the tube wall is found to be involved to a great extent, the transition between benign and malignant epithelium should be demonstrable. As mentioned before, it is important to distinguish between true neoplasm and the adenomatoid hyperplasia that follows tuberculous salpingitis (13).

Numerous microscopic classifications are seen in the literature, but basically the most commonly used is Hertig's modification of that proposed by Sanger and Barth (Table V). The modified one is as follows (4):

(a) *Grade I - Papillary*
- -lesion is confined to lumen of tube
- -the transition between normal and malignant epithelum is clearly seen
- -cells are fairly well differentiated (columnar)
- -few miototic figures

(b) *Grade II - Papillary -Alveolar*
- -beginning of glandular formation
- -some invasion of tubal wall
- -undifferentiated cells
- -moderate number of mitosis

(c) *Grade III - Alveolo - Medullary*
- -solid growth with lack of papillary projections
- -cells (undifferentiated) arranged in a medullary and/or glandular pattern
- -invasion of lymphatics of tube wall
- -vacuolization of cells with abundant and atypical mitosis

Though some authors believe that there is no correlation between the histologic pattern and prognosis (12), Hertig (4, 9) believes that this relationship does exist. He believes that the lower the grading, the better the prognosis.

TABLE V: MICROSCOPIC CLASSIFICATION OF TUBAL CARCINOMA

Grading	Localization	Type of Cells	Arrangement	Mitosis
I Papillary	-mucosa	-well differentiated		-scanty
	-good demarcation between malignant and normal mucosa	-columnar	-papillary projections	
II Papillary Alveolar	-invasion of tubal wall	-undifferentiated	-some associated with glandular formation	-moderate in number
III Alveolo Medullary	-invasion of wall with lymphatic involvement	-undifferentiated with vacuoles	-medullary and/or glandular pattern	-abundant and atypical

Tubal carcinoma metastasises by continuity, contiguity, transperitoneal migration, lymphatic and vascular channels. It is believed the metastasis occur usually before there is evidence of involvement of the tubal wall (9, 11). Invasion of the tubal wall is usually a late phenomenon (1). Hanton, *et al* (12) believes that there is no correlation between the gross size of the lesion and the presence of extent of metastasis.

In 35 cases reported by Sedlis, the organs involved in their order of frequency are as shown in Table VI. Contrary to the incidence of 11.5 percent of vaginal metastasis, Ross, *et al* (15) report a 60 percent incidence.

Mitchell, *et al* (1) believe that lymphatic spread is the most common way of metastasis. These may occur along the broad and infundibulo-pelvic ligament lymphatic channels as well as through the ovarian channels to the iliac, para-aortic and lumbar nodes. Spread may also occur along the path of the round ligament to the inguinal nodes. The organs that may be involved by lymphatic spread include the cervix, fundus uteri, ovary, vagina, bladder, kidney, liver, lungs, stomach, large intestine, diaphragm, skin and supra-clavicular nodes. Hematogenous spread may involve the liver and the vertebral bodies (15).

Diagnosis

The diagnosis of tubal carcinoma poses a difficult challenge to the gynecologist. In very few cases has the preoperative diagnosis been made (4, 11, 13). The difficulty in diagnosis is not only due to the rarity of the condition, but also due to the inconsistency of the signs and symptoms. It has been

TABLE VI: ORGANS INVOLVED IN ORDER OF FREQUENCY (11)

Organ or Site	No.	Percent
Peritoneum	35	100
Ovaries	22	63
Uterus	11	31.5
G. I. Tract	4	11.5
Vagina	4	11.5
Lymph nodes	3	8.6
Liver	2	5.7
Generalized	4	11.5

said (16) that the possibility of tubal carcinoma, in the presence of a positive cytosmear and a negative cervical biopsy and endometrial curettage, has to be strongly considered. Schenck (16) thus believes that such a situation is a strong indication for an exploratory laparotomy or at least for further diagnostic procedures. The positivity of cytosmears poses another real problem. Though most series report 0 percent of positive smears (8, 12), Sedlis (11) reports a 60 percent positive smears in 48 patients with tubal carcinoma. Other series report lower percentages (2, 8, 13). Sedlis, believes that bed rest and a cervical cap prior to the examination increases the positive yields because a positive smear depends on the following factors: (a) the surface of the tumor should be sufficiently large; (b) the abdominal ostium of the tube should be closed; (c) the isthmic portion of the tube must be open.

In view of the fact that very few cases were diagnosed pre-operatively, most of the working diagnoses of these patients included such as ovarian cysts, with or without twisted pedicles, salpingo-oophoritis, hydrosalpinx of unknown etiologies and uterine fibroids.

Some authors have advocated the use of culdocentesis as an aid in diagnosis. Hu (4) believes that a yield of hemorrhagic fluid with polyhedric fatty acids and degenerated cells is strongly suggestive of a tubal malignancy. Most authors agree that both culdocentesis and colpotomy are inconclusive (4, 15). Although there are some reported cases in which diagnosis was made by salpingography, most authors condemn this procedure due to the imminent danger of spreading malignant cells thru the fimbriated end of the tube (4, 15).

Hu (4) and Hayden (7) believe that with the more modern expectant treatment for chronic PID, more cases of carcinoma of the Fallopian tube will go undiagnosed until they reach an incurable stage.

In order to detect tubal carcinoma at earlier stages Frankel suggests the following indications for exploratory laparatomy (3): (a) at or after the menopause, when an obscure pelvic mass presents itself; (b) when symptoms of low abdominal pain, vaginal discharge or bleeding accompanying a pelvic mass presents at or after the menopause; (c) when inflammatory manifestations are present at or after the menopause.

Treatment

Due to the difficulty in diagnosis, fallopian tube carcinomas are quite advanced at the time of surgery. Most authors agree that the best surgical approach is a total abdominal hysterectomy with bilateral salpingo-oophorectomy (9, 11, 12). The use of more radical type of surgery is considered by some of dubious value (7) although there are reports with excellent results (18).

Sedlis (11) reviewed the different types of surgery with or without post-operative radiation (see Table VII).

Though the treatment of choice is surgery plus post-operative radiation, most authors seem to agree that radiation has done little, if any-

TABLE VII: METHOD OF TREATMENT AND RESULTS (11)

	Total Hysterectomy		Radical Hysterectomy		Sub Total Hysterectomy		Salpingectomy		Salpingo-oophorectomy		Total	
	Total	*5-Yr Survivors*	*Total*	*5-Yr Survivors*	*Total*	*5-Yr Survivors*	*Total*	*5-Yr Survivors*	*Total*	*5-Yr Survivors*	*Total*	*5-Yr Survivors*
X-Ray	69	11	3	0	19	5	8	2	29	8		
No X-Ray	34	3	1	1	19	5	2	0	5	0	191	35

TABLE VIII: RESULTS OF TREATMENT IN TUBAL CARCINOMA (8)

Stage	Total of Patients	Not Eligible for 5 yrs Follow - Up	Lost to Follow-Up	Died of Disease *	Survived five years	
					No.	*Percent*
I	14	4	1	2	7	70
II	5	0	3	1	1	20
III	4	1	0	3	0	0
X	2	0	1	1	0	0
Total	25	5	5	7	8	40

* - *Presumed dead of disease less than 5 yrs after treatment.*

thing, to improve the salvage rate (6, 12, 15).

With the advent of chemotherapy in the treatment of malignancies, few of these have been used in treating tubal carcinoma. These are: mechloroethamine HCL (Nitrogen Mustard); 5-Fluorouracil (5-FU); triethylenethiophosphoramide (Thiotepa); cyclophosphamide (Cytoxan).

Overall results seem to indicate that none of the chemotherapeutic agents used so far cause any significant regression of tumor mass in extensive lesions or adjust to the criteria for improvement of Curreri (20).

Harlbutt (19) believes that the chemotherapeutic agent of choice is N2 Mustard, to be used pre-operatively, while others report fairly good results with the use of 5-FU (20).

Survival Rates

Though values as low as 5 percent (6) and as high as 44 percent (12) for a 5-yr survival rate have been reported in the literature, the usual accepted and expected rates lie somewhere between 20-30 percent (7, 11). As already stated before, contrary to some au-

TABLE IX: PRIMARY CARCINOMA OF THE FALLOPIAN TUBE SEEN AT I. GONZALEZ MARTINEZ CANCER HOSPITAL

No.	Age	Gravity and Parts	Menstrual Status	Major Symptoms	Classical Triad *Pain*	*Discharge*	*Mass*
1	47	Gr_3 P_2 Ab_1	Menstruating	Lower abdominal and pelvic pain	Lower abdominal and pelvic	None	Right pelvic
2	61	Gr_2 P_2	Post-menopausal	Vaginal bleeding	None	Vaginal bleeding Coffee gr. vaginal discharge	Right pelvic
3	52	Gr_7 P_7	Post-menopausal	Vaginal bleeding - Abdominal pain	Lower abdominal	Vaginal bleeding	Left pelvic

TABLE X: PRIMARY CARCINOMA OF THE FALLOPIAN TUBE SEEN AT I. GONZALEZ MARTINEZ CANCER HOSPITAL: OPERATIVE FINDINGS AND TREATMENT

No.	Operative Findings	Treatment *Surgery*	*Radiation*	*Chemotherapy*	Pathology *Gross*	*Microscopically*	Follow-up (yrs.)
1	Right tubo-ovarian mass Right acute salpingitis	T.A.H. R.S.O.	None	N_2 Mustard (30 mg I.P.) ThioTepa (60 mg I.P.)	Information not available	Adenocarcinoma	Dead 1 1/2 yrs.
2	Bilateral adnexal masses	T.A.H. B.S.O.	^{60}Co (4500r)	ThioTepa (105 mg I.P.) ThioTepa (108 mg I.V.) Atabrine (.2 mg I.P.)	Right (13x7x5cm) Left (4 x 4 cm)	Papillary-medullary adenocarcinoma	Lost to follow-up at 4-1/4 yrs. (Dec. 67)
3	Bilateral hydrosalpinx Left ovarian cyst	LSO (7-8-63) ---------- Supracervical hyst. RSO Partial omentectomy Bil. ligation hypogastric artery (8-3-63)	^{60}Co (4000r	None	Information not available	Adenocarcinoma	Alive, 4-1/2 yrs.

thors, Hu and Hertig (4) believe that the salvage rate is closely associated with the pathological grading of the tumor. Dougherty *et al* (8) believe that this survival rate is also determined by the staging of the disease. Using the following criteria

Stage I - local
Stage II - spread to other pelvic sites
Stage III - spread to other abdominal and distant sites
Stage X - unknown

he showed the results shown in Table VIII.

It seems, therefore, following Hu, Hertig and Dougherty, that the results of therapy depend on the pathological grading and on the stage of the disease.

Patients seen at I. González Martínez Hospital

Three cases of primary carcinoma of the Fallopian tube were seen at the Isaac González Martínez Cancer Hospital, Río Piedras, Puerto Rico, in the years covered between January 1961-March 1968. Though cases 1 and 3 were not diagnosed primarily at this institution, they were included in the series because these patients received at least partial treatment for their disease at this hospital. The important clinical data and mode of treatment and results are included in the following tables (Tables IX and X).

The ages and menstrual status of patients reported are well in accord with that stated in the literature. Interesting enough, all of the patients were multigravidas including one grand multipara. This is in disagreement with the 50 percent nulliparity or low gravity reported in the literature. Interesting enough too, one of the patients had the classic triad of pain, discharge and pelvic mass. The other two had at least two of the components. The three patients had some type of pelvic mass.

All these patients received at least the accepted type of surgical treatment. Of interest is the fact that the two patients that received post-operative radiation have shown survival rates of over 4 years. Due to incomplete information, it was impossible to correlate pathological grading and staging of the disease with the salvage rates. It should be noted that in the two cases in which chemotherapy was used, there was clinical evidence of extensive and quite advanced disease. The value of chemotherapy at present is undetermined, but it must be mentioned, that in case 2 there has been evidence of advanced disease for at least 18 months and since then the patient has been maintained only on chemotherapy with fairly acceptable results.

Summary

Primary tubal carcinoma is the rarest of all gynecological malignancies occurring most often in females in the fifth and sixth decades of life. Though early manifestations are vague, vaginal discharge, lower abdominal pain and a lower abdominal or pelvic mass in a post menopausal woman should make you suspect this entity.

Occasionally positive vaginal smears are found and this, in association with negative cervical biopsy and endometrical curettage, should make the diagnosis of tubal carcinoma or at least suggest the possibility.

Due to the difficulty in diagnosis, the disease is usually quite advanced at the time of surgery, leading to poor salvage rates.

The overall value of each of the modalities of treatment is still under extensive evaluation.

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LACERATIONS OF HAND TENDONS:
A Review

José L. Borrero

It is necessary to stress the important role of the hand as a remarkably polyfacetic structure. Unawareness of this importance, perhaps, is one of the reasons why injuries to the hand are often mismanaged: an error that results in complications which are frequently crippling.

Hand lesions are some of the costliest single injuries in our nation today. They represent a tremendous expense to the nation's economy in the form of compensation for the disabled. The hand at present is one of the most frequent sites of trauma: Industrialization and mechanization has made it so (5).

Injury to the hand is in essence a surgical problem in specialized tissue healing. It demands sound knowledge of its surgical anatomy, full awareness of the complications that may arise, and a sober capacity to individualize each case.

This paper is limited to nerve and tendon lacerations. Both the physical evaluation and the management of such lesions will be reviewed. The application of the new field of microsurgery to hand surgery will be included.

A great number of hand injuries are lacerations to the tendons and nerves, or both. Division of tendons and nerves is usually followed by contractures and adherences, which result in greater impairment of hand function than that occasioned by the original injury.

Extensors

In the majority of the cases, repair of the divided extensors does not represent a major surgical problem, and results are good. Various reasons can explain this:

1. Anatomically extensors flatten as they reach the phalanges, spreading out and inserting over a relatively wide area, thus decreasing the probability of complete tendon division.
2. Both range of motion and strength are less for extensors than for flexors, allowing for a less complicated recovery and post-operative treatment.
3. The loose tissue surrounding extensor tendons does not allow for the rigid adhesions found in the volar aspect of the hand.

In addition, major injuries in the dorsum of the hand are less common than those involving the flexor tendons. On physical examination, division of an extensor tendon is considered when there is inability to straighten the fingers or the wrist. A finger with a completely divided tendon will be mildly flexed, as in the position of function. Primary repair is recommended in most occasions of extensor tendon division.

Flexors and Nerves

Division of the flexor tendons is the most important and most common lesion occurring in the hand. Unlike extensors, injury to the hand flexors often produces sad results.

Injuries to the nerves in the hand are also

quite eommon and perhaps too frequently have disabling implieations. Moreover, eombined nerve and tendon lesions are so eommon that they will be eonsidered as one in this paper.

Physical Evaluation

Adequate initial evaluation in the Emergeney Room is erueial in the treatment of flexor tendon injuries. Two faetors should be defined as exaetly as possible: A) The extent of the lesion; B) The loeation of the lesion. During this evaluation, hemorrhage should be eontrolled by a pneumatie tourniquet, and not by instrumentation (7).

Extent

Sinee the extent of the lesions ean be determined by the alterations in funetions, it ean be summarized as follows:

Tendons: Inability to flex distal phalanges implies division of the flexor pollieis longus or the flexor digitorum profundus. Inability to flex the injured finger when the uninjured fingers are held baek in maximum extension by the examiner implies division of the flexor digitorum superfieialis.

Median Nerve: The inability to toueh the tip of the thumb to the tips of the other fingers as if pineling implies loss of thumb apposition, a median nerve funetion. The loss of sensation in the volar side of the hand and digits I, II, III or the radial side of digit IV is found in median nerve division. It should be remembered that sinee lumbriealis museles III and IV reeeive ulnar inervation, in median nerve paralysis these are not affeeted and a "preaeher's hand" results.

Ulnar Nerve: The inability to spread the fingers is an easy method to determine ulnar nerve injury (motor branch to interossei). Loss of sensation of the dorsal of volar areas of digit V and the ulnar half of digit IV implies a strietly ulnar nerve division. Also, inability to slide or serape the thumb aeross the palm indicates a non-funetioning adduetor musele of the thumb, which reeeives ulnar inervation. This finding implies either division of only the ulnar braneh to the adduetor, (in whieh ease sensation and finger spreading should be normal) or division of the ulnar nerve proximal to the ulnar bifureation with eoncomitant loss of sensation and finger spreading ability. Conversely, loss of ulnar sensation and finger spreading with adequate thumb adduetion implies ulnar nerve division distal to the ulnar bifureation, thus distal to the braneh to the thenar eminenee. This braneh usually travels together with the deep arterial areh in the palm, henee proximal to the superfieial arterial arch and also proximal to the proximal palmar erease. Ulnar nerve palsy is eommonly described as the simian hand.

Radial Nerve: A dropped wrist is indieative of radial nerve division. While the loss of sensation radially from the middle of the fourth finger of the dorsum of the hand is seen in radial nerve palsy. A good way to evaluate extensor and radial nerve division is to instruet the patient to have both palms touehing eaeh other with fingers straight, (as if praying), and to try to separate the finger tips without bending the fingers or separating the palms. Division of the radial nerve or of some of the extensor tendons will not permit the patient to separate the finger tips.

Location

The anatomical loeation of the injury is important sinee eertain areas of the hand require speeial attention when surgieally intervened. These areas are: 1) the digital sheath area; 2) the wrist area; and, 3) the area distal to the insertion of the flexor sublimis tendon. The rationale in the management of injuries oeeurring in these speeifie areas will be diseussed under treatment.

Repair of Tendon Injuries

A review of the literature clearly indicates that there is a great number of methods utilized in the repair of flexor tendons. Results, however, do not prove the supremacy of any one particular technique. Regardless of the method utilized, a surgeon should strive to restore the three main functions of the hand which are: grasping, feeling and pinching (19).

Extent and location of the injury, the two factors mentioned during the physical evaluation, will again be of primary concern during repair. As mentioned before, there are three different sites of injury which require special consideration. Surgical repair should differ in these areas since the surrounding tissues and hence wound healing, is not the same. Thus, the problem of hand surgery in essence becomes a problem of specialized wound healing.

Primary vs. Secondary Repair

The decision between primary and secondary repair has been a long standing debate among hand surgeons. In general, very rigid requirements must be met for primary repair.

Littler (16, 17) and others have recommended primary repair when a laceration is sufficiently distal, so that during flexion, the tendon suture line does not pass under the bridge formed by the division of the sublimis before insertion. He also advocates a wound no more than four hours old, and all the facilities of a major operating room.

Chase, on the other hand, states that "with the exception of skin and vascular anastomosis, there is no structure in the hand that cannot be successfully repaired in a delayed primary of secondary operation" (7). Therefore, most surgeons adopt the general rule of always utilizing secondary repair in lacerations between the distal palmar crease and the proximal interphalangeal joint, the so called no man's land or digital sheath area. In patients under eight years of age, primary repair is justified at any level (19).

While repairing injuries located in the three areas mentioned above, it must be kept in mind that regardless of the area, the immediate objective in repair is to restore tensile strength between tendon ends.

Repair distal to the insertion of the flexor sublimis: According to Peacock and Hartampf (19), there are various modes of treatment for lacerations in this area. These include:

1. primary or secondary repair by direct suture of divided ends, or by advancement of the proximal end of the divided tendon to the terminal phalanx;
2. tenodesis of the distal interphalangeal joint by fixing the distal stump of the profundis tendon to a more proximal structure, such as the sublimis tendon of middle phalanx;
3. fusion of the distal interphalangeal joint;
4. reconstruction of the flexor mechanism by the insertion of a free, full length tendon graft from the region of the lumbrical muscle in the palm to the base of the distal phalanx.

Repair within the digital sheath: It is in this particular area that the decision between primary and secondary repair has been mostly debated. With this, the following points have been reported:

1. excellent results have been obtained with both methods;
2. neither method offers completely satisfactory of uniformly excellent results;
3. primary repair demands very strict requirements, which are not feasible in most cases.

In secondary grafting, a portion of the palmaris longus, the best tendon source available for grafting, is attached to the proximal profundus at the level of the palm. The other end is secured to the distal phalanx or to a

profundus stump, preferably with the Bunnel pull out wire technique. Further discussion of the procedure is beyond the scope of this paper.

Repair at the wrist level: Again the question of primary vs. secondary repair comes up in this area. Peacock (19) states that primary repair may be achieved in optimum conditions without difficulty, but that lesions at the level of the carpal ligament should be repaired secondarily. Chase (7), on the other hand, points out that an attempt to repair all structures at the wrist primarily is incorrect and detrimental. He also states that skin and soft tissue should be repaired initially, followed by the tendons of the flexor profundus, and the flexor pollicis longus median and ulnar nerve repair in one operation. Thus, it is advocated to leave the following structures unrepaired: a) flexor carpi ulnaris; b) flexor carpi radialis; c) flexor digitorum superficiales; and, d) palmaris longus.

Another point of argument is the repair of both profundi and sublimis tendons in wrist injuries. Peacock (19) points out that it makes no great difference whether the sublimis tendon is repaired or discarded. One of the drawbacks of repairing both sublimis and profundus is that the tendons may adhere to each other, causing limitation of motion of the profundis, since it has a greater range of motion. This, however, occurs in very few cases. On the other hand, the incidence of recovery of independent sublimis action is also very small. Convenience for the surgeon, as well as decreasing tourniquet time, are factors in favor of profundus repair alone.

When considering repair of flexor tendons as a whole the following outline from Chase (7) is very helpful:

I. Division of profundus only
   a. 1 cm from insertion: Resinsertion, primary repair.
   b. Distal to the decussation of the superficialis: Bunnel's pull out wire technique by primary repair.
   c. In the digital sheath: Secondary tenodesis in the distal joint.

II. Division of profundus and superficialis
   a. At wrist level: Primary profundus repair.
   b. In the digital sheath: Primary skin repair. Secondary full length graft for profundus only.

III. Superficialis only
   a. At any level: Primary repair of skin, neglect tendon.

Microsurgery

The advocates of microsurgery have given a new dimension to hand surgery. At present digital reimplantation has been achieved by Tamai (2), while others have obtained discouraging results, mainly due to vascular failure. The importance of microsurgery is established by the fact that it has been shown that the successful transplantation of most of the tissue components rely on the integrity of blood vessels under 2 mm (21).

It should be remembered that blood vessels of 3.0 mm outside diameter and less are usually found in the fingers. By definition, these are considered microvessels, hence demand the use of a microtechnique in their repair. It has been shown that the distribution of the vasa vasorum in the microvascular tree is responsible for some of the failures in anastomosis. These vasa vasorum are contained within the adventitious sheath enveloping the small arteries supplying the fingers. Peeling the vessel of its sheath thus disrupts the continuity of the vasa vasorum, and consequently the healing process at the site of anastomosis. If the blood vessels lack circulation they will behave as a free graft, until their circulation is restored by the ingrowth of blood vessels. There is a difference, however, in the location of the

vasa vasorum between arteries and veins. In veins, stripping of the surrounding areolar tissue appears to only partially deplete the wall of its circulation.

Under a microscope, with special monofilament nylon 9-0 or 10-0, mounted on taper point needles, blood vessels of a diameter of 1.0 mm (slightly larger than a gange 30 needle) have been repaired.

It is thus feasible to believe that once the rejection phenomenon is controlled, digital transplantation using the technique of direct vascular anastomosis will be achieved by a properly trained surgeon.

The microtechnique is obviously also applicable to the repair of peripheral nerves of a small diameter. A complete functional reimplantation is achieved in this way. Precise alignment of the severed ends and consideration of the blood supply of the nerve running along the mesoneurium explains the good results obtained so far.

A complete review of the techniques involved in a microsurgical procedure are beyond the scope of this paper. Reference is made to the bibliography (21, 22). The logical conclusion, however, is that to obtain results that near perfection, hand surgeons must adopt the microsurgical techniques.

Summary

Today hand injuries represent a surgical problem of tremendous importance requiring special surgical management.

In the physical evaluation of lesions producing division of tendons and or nerves, two factors must be defined: the extent and the location of the lesions. Specific characteristics of various injuries were reviewed under this section.

The decision between primary versus secondary repair of divided tendons was discussed. The established modes of repair for lesions localized in the sheath area, the wrist area, and distal to the insertion of the sublimis tendon, were reviewed.

A brief discussion of the new field of microsurgery and its application to hand surgery concluded the review.

Resumen

Hoy en día las lesiones en la mano representan un problema quirúrgico de tremenda importancia que requiere un manejo especial.

En la evaluación física de lesiones que producen división de tendones y/o nervios hay que considerar dos factores: la localización y la extensión del daño. Características específicas de varias lesiones fueron descritas bajo esta sección.

Los factores a favor y en contra sobre la decisión de suturar lesiones de tendones por intervención primaria o en una segunda intervención, fueron discutidas. También se repasaron varios métodos de reparar lesiones localizadas en la vaina del tendón, el área de la muñeca, y en el área distal a la inserción del tendón superficial.

Se concluyó este repaso con una discusión breve sobre la microcirugía y su aplicación a la cirugía de la mano.

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ON PSYCHOTHERAPY

Víctor Bernal y del Río, MD

I shall bring forth examples for which I am indebted to residents who have worked closely with me at one time or another. Elsewhere, drawing mostly from experiences in my own practice I pointed out certain particulars of psychotherapy in Puerto Rico. Most of the examples and resultant ideas herein are drawn from material of patients presented to me in group supervisory sessions. In an attempt to stabilize some kind of curricula for the difficult tasks of teaching psychotherapeutic techniques, besides other didactic teaching in the curricula which are not our concern today, I divide the supervisory or controlling experience into two different spheres: One—individual supervision which entails a microscopic study of the patient-therapist relationship with particular emphasis on the transference counter-transference phenomenae. This usually should be preceded by a thorough evaluation of the therapist's inner conflicts, scotomas, etc., possibly with the help of a personal analysis. I name this type first although it should come last in schedule and again is not our primary concern today. Number two—group supervision in which three or four residents present a case to a training supervisor once a week. The case is presented three continuous months by each of the residents of the group. I must underline the importance of the group being fixed or structured in the sense that visitors or newcomers are not allowed, absences are discouraged and the meetings take place at the same hour every week. In these particular groups the choosing of the patients has been done by the residents themselves, upon referral from different sources in the community, with very little supervision of the choice or the contracting previous to the presentation of the case. The group supervisor occupies himself mostly with strategies, tactics and maneuvering, management of specific situations, silences, absences, lateness, phone calls, scheduling, written material, etc.

Looking backward at my experiences with six groups of residents who presented 17 cases, the first thing that calls my attention is the fact that all cases presented were seen once a week. This, in spite of the fact that there was complete freedom by the residents in the selection of patients from, it is true a rather small waiting list and that there was absolute freedom in the scheduling of the psychotherapeutic procedure. Such stereotype of frequency is to be noted and calls for some commentaries. Any stereotype of a particular schedule is paramount to a freezing of the psychotherapeutic procedure, its goals and vicissitudes. As such freezing is not desirable some reasons must be proposed for its constant occurrence. Perhaps the difficulty in setting criteria of frequency itself could be the

Paper read in October 12, 1967 at the annual meeting of the Section of Psychiatry of the Puerto Rico Medical Association.

reason for the tendency of the beginner, to assign himself a fixed frequency always. It seems to me that all criteria of frequency must take into consideration diagnosis, chronicity and perhaps the dramatic and incapacitating aspects of the symptomatology besides the goals of therapy. Goals per-se of a reconstructive nature demand certain frequencies and prolongation by which we all have to abide. Modification of frequency, must open the questions for modification of goals. If such is not the case the therapist may find himself in a position of trying to do the impossible with the ensuing frustration — the process gets rapidly into a stalemate and the patient flees. In some instances I look upon frequency as a stipulation of dosage, and it is not for the patient to have the final decision on such obvious medical procedure.

Apparently one of the mechanisms present in this tendency is the "urge to cure" "to see everybody that calls combined with a great "medical zeal". In these groups the occurrence of the once a week has to be interpreted also as a reaction to the supervisor who by being a psychoanalyst and thus an "intensive therapist" — may have created in the trainees an ideal of the ego of such dimensions that any imitation or identification is automatically rejected in practice. The therapist tends to accept the patients rationalizations in terms of "difficulty in travelling", "lack of funds", etc. The zeal to cure, to try out, etc., sometimes lead to the selection of the frequency by the patient rather than by the therapist and also by the symptoms rather than by the process.

The need for "acceptance" on the part of the therapist leads to a tendency to "try out" which leads to a trial at carrying over their shoulders a burden of such dimensions which only a herculean ego could support. The tendency to brief contacts or minipsychotherapy, as some prefer to call it, has to be interpreted also as a fear of a too intimate relationship, closer by the numerous contacts and the fear of emotional involvement with the patient. It becomes a mechanism to keep the patient at an uninvolved distance, apart.

The therapist's need for acceptance often clouds his prospective goals for a particular patient.

The desire for a so called "big practice" meaning numerous patients and to be "well known" and "popular"; the desire to be able to say yes to every request of patients and the difficulty in turning patients down have to be investigated, as these are more therapeutic for the therapist's "need of recognition", "fears of starvation", etc., than for the patient's needs.

It seems that more psychotherapy has been done at this magic interval of once every seven days than at any other and of course, the magic of the number seven has to be taken into consideration. Once every seven days looms inescrutable over mankind, including psychotherapists.

The amount of time per interview was assigned almost automatically at a 45 or 50 minute hour in a very direct emulatory movements of the supervisor, in contrast with the opposite negative identification of the frequency pointed out earlier.

It is my firm belief that beginning therapists in the supervisory circumstances should experiment in all phases (*i.e.* frequency, time, etc.) of the therapeutic situation. Hopefully all possible mistakes will be done while under direct supervision, as unfortunately this is rather short lived in our present setting.

All patients presented were seen in a sitting up position with the therapist more or less facing the patient.

In most cases continued hand shaking was reported at every interview more frequently at the beginning of the hour than at the end. In contrast in my own practice hand

shaking if at all present usually disappears rapidly except for one or two experiences of continued hand shaking during prolonged courses of therapy. Even in hand shaking procedures changes can be microscopically noted. I am not only referring to strong or weak hand shakes but to the noticing of particularities in the hand itself; hurried, cold, warm, the position of the extended hand (*i.e.* waiting for the other hand in a high or low position) palm facing upward or downward or strictly vertical or with the use of the second hand in the shake.

Some ethnical or cultural differences have to be taken into consideration but the patients were all of Puertorrican extraction.

The method of the taking of notes was in every case a matter of great concern to the therapist because of a redundant need for efficiency and a too great "desire" to bring the material "as occurred". It goes without saying that quoting the patient is easier than quoting oneself and thus special consideration should be impressed in the resident to bring the verbatim of his interventions as well as the patient's. Ideally, each resident should take a trial at writing during the interviews, immediately after the interview, much later, presenting "from memory", taping, video taping, etc.

Not one lateness of therapist or patients was reported in the 17 cases nor were there examples of absences of the therapist! Confusions in the scheduling on holidays were very frequent which appeared with the ensuing management parameters in every group and which gave the group the opportunity to discuss communications with the patient by phone, letters or the peculiarities of instructing third parties communicating in the name of the therapist.

Written material (*i.e.* poetry, stories, written dreams, autobiographical material) was brought to therapists with a rather great frequency and the natural tendency of the therapist to keep material for further perusal when time permitted, which rarely occurs (had to be pointed out). This, of course, multiplies the time given to such a patient who becomes a "preferred patient". It had to be worked through in supervision continuously, as the tendency to "benevolence" is rather great in our residents. The technique of asking clear questions had to be revised over and over. The double and triple questions appeared often. The question that changes direction in the middle of the stream.

The questions in which any answer but the obvious would shade doubts as to the individual's capacities, decency, etc., occurred in our groups.

The former is encountered frequently by the automatic use of the well known questions to elicit feeling, "and how did you feel? ". Upon the recollection of historic traumatic experiences as death of father, catastrophe, etc., to ask point blank "and how did you feel" in paramount to an insult unless the patient answers the obvious. Until the patient has acquired some kind of idea of the eliciting characteristics of the process such questions amount to a direct intent at exploration of splitting. Such is, perhaps, the only exception; in diagnostic interviews for differential diagnoses of borderline or ambulatory schizophrenia with great care such could be asked. The other exception is, perhaps, in a case already diagnosed to probe into the ego strength in which the capacity to deal directly and openly with historical ambivalence and day by day splitting may give a clue as to ego stature or the capacity for reintegration.

The double question is an occurrence that may be difficult to detect and or specifically to self identify.

We mean by double question situations in which the therapist, in an attempt many times to collect a formidable amount of data, is

carried away and introduces in the middle of formulating a question another question complicating the issue in such a way that you have a bewildered patient not knowing where to start and how. In some cases the changes occur as an intent at clarification of the question. But the result is the same: "What do you remember of your father? ". "How was he? ".

To my surprise silences were not reported frequently which I consider a phenomena. As it is usual in our discipline the absence, or not reporting, is per-se a phenomena to be explored and questioned. Thereafter, silence became an important part of our considerations.

Silences are part and parcel of every psychotherapeutic procedure. They point out to the particular specified set non "social" situation. The therapist must train himself to be able to sustain silences without undue anxiety marring the process.

His weighted waiting has to be devoid of too much changing position, fidgeting, etc., of which I will say more later. It is a good training device to try to guess the time that has elapsed in a silence and check it against the inexorable of the minute hand.

In supervision I always instruct the trainee to bring the number of silences and the material preceding and proceeding the silence.

Besides silences I instruct the resident to be aware and report movements in the patient and if possible in the therapist himself. Silences have to be regarded not as a cessation of communications but as a change in the type of communications from verbal to non verbal. The non verbal communication increases with silences at the verbal level and as it becomes the sole type of communication it is easier to detect. In supervision we deal separately with silences in the patient and silences in the therapist. I advise beginners in psychotherapy to wait with the silent patient or with any silence in any patient, until they detect some movement and when they detect some movement no matter how minute, only then to interfere verbally. In this way what the therapist is doing is reinstating the verbal communication and not starting the communication. The real silent patient both at a verbal and non verbal level with the absolute absence of any kinetism will not respond to proding, questioning or any other attempt on the part of the therapist. In the observation to detect movements of the patient before interfering special notice should be given to the muscles from the head to the trunk muscles or the throat, especially swallowing. With the carrying out of this recommendation we have found very few non responding patients.

The completely silent therapist has not been an occurrence of frequency in these residents. This is a rather frequent phenomena in many training facilities on the continent. It is often due to the close identification with the supposedly silent analyst.

It is also a way of saying: "If I don't say anything I can't err and thus nothing can be pointed out to me in supervision".

The silent therapists do sometimes present themselves in a modified form. By following strictly only one of the obvious rules of intervention (Why?) after every sentence of the patient or the tedious repetition of the last word of the patient they try not to make mistakes — it is usually so repetitive and frequent that is easily detected.

Apparently, the completely silent patient did not occur in this group of patients and I wonder if it is of rare occurrence in Puerto Rico. The difficulty with non verbal communication, especially movements, is the difficulty in their interpretation. The advantage with verbal communication versus non verbal communication is that it is more precise in its meaning, needs less interpretation, leaves less margin for errors. The clarity of the

verbal message is really portentous in spite of all its' nuances when compared to the non verbal. It is not strange that non verbal, although pointed out in every textbook, is rarely gone into or spelled out in its' use (or usage).

A silence together with real immobility including complete absences of kinetism is a real silence of such nature that communication has ceased to exist, and in such, starting communication is something completely different.

In proposing that the therapist wait without interfering verbally for the appearance of such phenomena which I include in kinetism what I am proposing is a waiting period to let the non verbal communication start on the part of the patient and thus the intervention of the therapist is nothing but a reinduction, a redirection, into the verbal of the already started communication. This can be done even without knowledge of the meaning of the non verbal message. All we know at present is the patient is trying to "say something".

I include in kinetism such phenomena as resemblances in the position taken by the therapist, patients. Resemblances of position of hands, feet, accompanying gestures, micromovements in the therapist and in the patient. The relationships between similar movement in patient and therapist is what I prefer to call microechopraxia.

Movements, both conscious and unconscious, awareness of a desire to move and the almost mental representation of the movement are also part of kinetism.

As psychotherapy should be carried out in a "controlled" situation of position and movement (this is the parallel of the verbal silence of the therapist who should also be silent with his body and in whom movements of change of position for physiological reasons should be numbered, cognious and deliberate). In such a situation the therapist becomes the observer of himself, seriously aware of a vast empire of movements — the observation of which can easily be detected in films of interviews which are being studied in many parts of the continent: Cleveland, Pittsburgh, Chicago, etc.

I tell young therapists "be aware of your body". The therapist will discover movements in himself of which he is not aware at the time of their occurrence but is aware shortly after. The therapist who observes himself rather carefully will become aware of certain tensions in certain muscles or groups of muscles which if translated into movement would bring about a certain particular movement — the therapist will also become aware of micromovements in the patient. These are some times echoes of his own micromovements' responses to them, sometimes mirror like images of them and must be considered in such a relationship. Notice should be taken also if the verbal intervention of the therapist to break a silence (which should be short, precise and non directive) is answered or responded to by a movement of the patient before he resumes verbal communication.

You may notice that I am talking of movements in the patient in general without specification of the movement per-se.

The movements I am talking about and which are more useful are not changes in position, fidgeting or stereotyped movements such as desk beating, knee dancing, etc., but rather small movements. To determine the meaning of a movement of upper or lower limbs towards the therapist or away from the therapist, towards the center of the body or away from the center of the body, etc., is not our concern today.

"Imitation", said Aristótele in "The Poetics" is "natural to man from childhood". We are all familiar with the resemblances between spouses of long standing. Children reared by foster parents without any blood relationship tends

to resemble the foster parent because they "copy" some of the movements, positions, gaits, etc., of the foster parents. We all know from psychoanalytic theories of development that "the primitive perception is characterized by being very near the motor reaction. At the beginning the first motor reaction is equal to the first perception". Idea, perception and movement are the same.

In psychology, starting with Henry James, the ideas of observations of the self are closely related to observation of movements.

Quoting from Alport, he says: "Some motor mimicry appears to precede and to be a precondition of learning. It is obvious that the process of perception itself entails motor adjustments that are "imitative" of certain properties of the perceived object".

Leaving apart the sterile concept of beauty in the study of art appreciation and trying to apply themselves to the study of the aesthetic experience instead, the aestheticians of the end of the last century leave with us some very interesting ideas and I am quoting Karl Gross— 1892— "The kernel of all aesthetic enjoyments is the activity or play of inner imitation whereby we imitate internally the mental or material features of an external object".

Lipps — 1893 — in describing the empathic experience in connection with viewing a Doric column was fairly explicit as to the existence of real movement and sensation — "the column seems to gird itself and erect itself, that is to say, to proceed in the way in which I do when I gird myself up and erect myself, or remain thus tense and erect in opposition to the natural innertness of my body. It is impossible for me to be aware of the shape of the column without this activity seeming to exist in the shape I am thus aware of".

"Beauty and Ugliness", published in 1897, insist upon the idea of mimicry as follows: "these movements of the line of an arch are in fact our movements in looking at the lines, movements in most cases so slight as to be barely perceptible".

Bernard Berenson, talking about what he called tactile values include specific examples of sensations and movements evoked by specific works of art; of two men wrestling he says, "unless my retinal impressions are immediately translated into images of strain and pressure in my muscles, of resistance to my weight, to touch all over my body, it means nothing to me in terms of vivid experience. . . What pleasures to be able to realize in my own muscles, in my own chest, with my own arms and legs, the life that is in him as he is making his supreme effort. . . "

To sit down to recall, to re-live, to emote, could be paralleled through the motor theory of thinking to the reactivation of a vast empire of experience by means of the implicit activity of the muscles originally involved in that experience. It is not parenthetical to evolve from this idea, very superficially presented, that inter-relation of movements between therapist and patients are of the utmost importance and could serve in establishing criteria for transference and counter-transference phenomena and even through the capacity for mimicry, imitation and empathy for the almost impossible task of prognosis in the achievement of the set goals of psychotherapeutic procedure.

Thinking about someone elicits an intent at internal imitation of the thought object we not only think, recall, and emote with our mind but with our whole body.

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CRYPTOCOCCOSIS COMPLICATING MULTIPLE MYELOMA

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In recent years it has been recognized that chronic diseases of the reticuloendothelial system, carcinoma, diabetes and others predispose to mycotic infections. Among five cases of cryptococcosis reported by Harland (1) in Canada, four of the patients had disseminated infection, including meningoencephalitis, two had Hodgkins disease, one had polycythemia vera and two diabetes. Kent and Layton (2) reported two cases of cryptococcosis with massive pulmonary involvement, and both patients had been treated with corticosteroids, one for acute lymphatic leukemia and one for hepatic cirrhosis, prior to the pulmonary and disseminated cryptococcosis. Zimmerman and Rappaport (3) have reported 60 cases of Cryptococcus infection from the files of the Armed Forces Institute of Pathology revealing a high incidence in association with Hodgkins disease and related disorders of the reticuloendothelial system. Symmers (4), in his recent paper on deep-seated fungal infections makes reference to 33 cases of cryptococcosis in an 18-year experience in the histopathologic laboratory service of a medical school in Britain. He describes one case of multiple mycotic septicemia in which Hodgkin's disease was widespread and treated with cytotoxic drugs and corticosteroids. The patient showed Cryptococcus pneumonia and dissemination of the fungus at autopsy. In experimental cryptococcosis Levine, Zimmerman and Scorza (5) were able to produce the disease by subcutaneous, intracerebral and intraperitoneal inoculations using various strains of *Cryptococcus neoformans*. Lesions of the brain were attended by proliferation of the yeast cells to form large focal areas with little inflammation and systemic dissemination. Systemic spread of the disease resulted from the use of cortisone in the subcutaneous inoculation with *Cryptococcus neoformans* which was also accompanied by an abolished inflammatory response.

This case report has a twofold purpose: first, the rarity of disseminated cryptococcosis and second, that to the best of our knowledge a similar case has not been reported from Puerto Rico. The rarity of disseminated cryptococcosis can be inferred by the fact that the present case is the only one of this nature among 1179 consecutive autopsies in the files of the pathology service of this hospital as of May 7, 1968.

Case Report

Multiple myeloma was first diagnosed on this 68-year old man in August 2, 1963. He was readmitted to this hospital for the third and last time on November 28, 1964. He had been doing well until September 1964 when he developed generalized aches and bone pains. Presently the patient was in no acute distress but appeared pale and chro-

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nically ill. The heart was essentially normal. The liver and spleen were not palpable.

The white blood cells count was 9,350/cu.mm with a shift to the left in the neutrophilic series. The red blood cell count was 2.48 millions/cu.mm, the hematocrit 24.8 percent and the hemoglobin 6.5 g/100ml. The platelets appeared adequate on dry smear. Urinalysis showed a 4+ albuminuria, 1-3 hyaline casts. The blood urea nitrogen was 20.8 mg percent and the serum creatinine 2.2 mg percent and calcium 10.7 mg percent. Examination of the urine for Bence Jones protein was negative. The serum protein electrophoresis was as follows: albumin, 56.28 percent; alpha I, 7.03 percent; alpha II, 11.56 percent; beta, 17.08 percent; gamma, 8.04 percent.

Radiography of the chest taken on November 30, 1964 showed osteolytic myelomatous involvement of several ribs and the left clavicle with clear lung fields. Skeletal survey, including chest, pelvis, skull and humeri on December 1, 1964 showed progression in the osteolytic involvement particularly of the bony structure of the thorax and pelvis. Similar myeloma lesions were present in the skull, humeri and scapulae.

The patient was placed on melphalan 2 mg three times a day and analgesics for control of pain. On December 21, 1964 he experienced chest pain associated with nonproductive cough and had moderate leukopenia and thrombocytopenia. Melphalan therapy was discontinued and treatment was initiated with procaine penicillin, prednisone 40 mg per day and blood transfusions. Chest X-Ray at this time revealed pneumonitis of the left lower lobe. The patient improved under this regime and 14 days later X-rays revealed resolution of the previously described pneumonic infiltration of the left base. He continued doing well until January 17, 1965 when he developed a febrile course and complained of severe generalized bone pains and a nonproductive cough. Throat culture taken at this time revealed *Pseudomonas aeruginosa.* The patient persisted with high temperature for the next two days in spite of chlortetracycline therapy. On January 20, 1965, while in the bathroom the patient suddenly collapsed and expired.

Pathology:

The body was that of an emaciated 68-year old, white male who weighed 106 pounds. He presented purpuric patches on the chest and upper extremities. The superficial lymph nodes in the neck were enlarged and palpable. The lungs lay freely in their respective pleural spaces. Subpleural hemorrhages with a lobular distribution were noted in both lungs. The pulmonary tissue was gray pink and doughy in the upper lobes of both lungs and congestive changes were evident in the lower lobes. The tracheobronchial lymph nodes were enlarged and soft. The lymphoid substance appeared replaced by a pale gray mucinous tissue. The nodes ranged in size between 1 and 3 cm in diameter. The heart was of normal size and its cavities and valves were not unusual. The abdominal cavity was free from fluid and was lined by a smooth and glistening serous membrane. The organs in this cavity were of normal size and general appearance. The spleen weighed 80 grams and presented a normal appearance. The endocrine glands showed no abnormality. The brain was of normal size and weighed 1350 grams. The cerebral hemispheres were symmetrical. There was no evidence of an exudate in the pia-arachnoid over the cerebrum and cerebellum, and that over the brain stem was thin and transparent. Serial cross sections of the brain showed no evidence of pathologic alterations of the nervous tissue. Examination of a good number of bones of the skeleton like the clavicles sternum, several ribs, lumbar vertebrae and iliac bones showed destructive defects in which the marrow cavity was filled with a reddish gray mucinous material.

Microsections from the left and right lungs stained by H & E showed many yeast-like cells in the septal capillaries, pulmonary vessels and within histiocytic macrophages in the alveolar spaces. There was a minimal inflammatory tissue reaction to the fungus cells. The PAS tissue reaction demonstrated a PAS positive polysaccharide capsule and budding of many of the yeast fungus cells. The Gomori's silver methenamine impregnation depicted to a better advantage the fungus and their budding reproductive activity (Fig. 1). A primary nodular lesion of cryptococcus was not identified in either lung. The tracheobronchial lymph nodes showed a severe lymphocytic depletion of the corticomedullary substance with a microcystic-like appearance. The nodal spaces were filled with a PAS positive capsular-pink staining reaction of the yeast-like fungus cells (Fig. 2). There was a slight inflammatory reaction to the fungus cells which were also easily demonstrable by the Gomori's methenamine silver stain. The spleen showed reactive fibroblastic thickening of the splenic cords, lymphocytic depletion of the malpighian bodies, the presence of myeloma cells in the sinusoids and discrete tiny cystic-like spaces containing the *Cryptococcus*

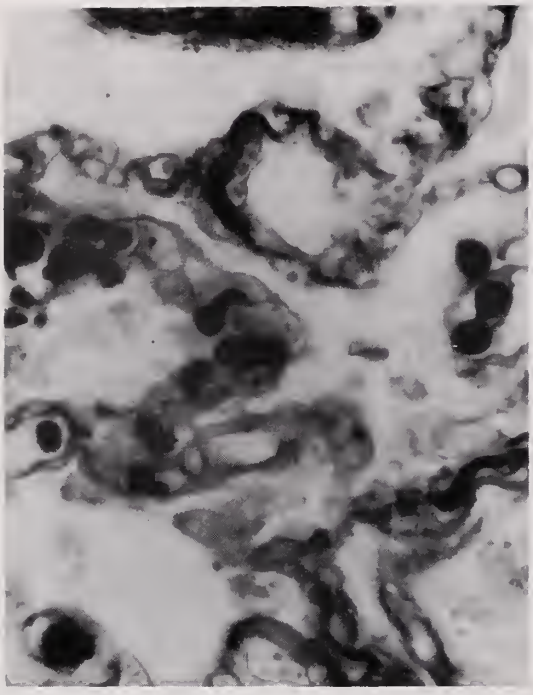


Fig. 1. Pulmonary cryptococcosis: Yeast fungus cells are shown in capillaries and alveoli. Budding of few of the cells is evident. Gomori's silver methenamine stain. Magnification X800.

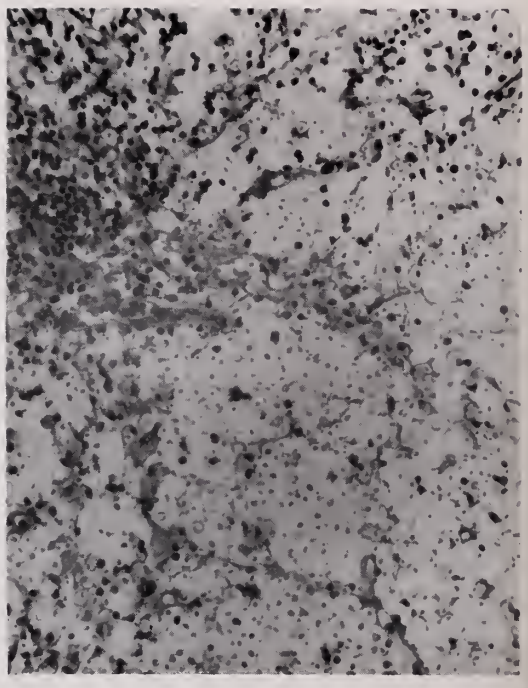


Fig. 2. Tracheobronchial lymph node stained by Mayer's mucicarmine method. Invasion of the nodal substance by numerous fungus cells with the formation of irregular spaces containing the fungus with a distinguishable capsule even at this magnification of X200.

neoformans demonstrated by the PAS positive staining of the fungus cells. Bone marrow from ribs, sternum, thoracic and lumbar vertebrae showed myelofibrosis and areas infiltrated with myeloma and plasma cells. The Cryptococcus cells were also demonstrated in the medullary substance of the marrow (Fig. 3). The fungus was present in the blood vessels and glomeruli of the kidneys, and in blood vessels of the adrenals. Microsections from the right frontal lobe, centrum ovale and right occipital lobe, from the corpus striatum, midbrain, cerebellum, pons and upper medulla were not remarkable. None of the brain sections showed evidence of medullary nor of meningeal cryptococcosis.

Discussion

The gross pathologic findings in this case were of a bilateral pneumonitis with a mucinous appearance which was interpreted at the autopsy table as a Pseudomonas or Pneumococcus bronchopneumonia. The regional tracheobronchial lymph nodes were enlarged and their substance appeared partly replaced by a pale gray mucoid tissue not unlike that seen in metastases of a colloid carcinoma. It was not till the study of the histologic sections that one of us became aware of the Cryptococcus infection of the lungs and lymph nodes and its dissemination.

Mycologic examinations were not done antemortem nor at the autopsy table because the pulmonary fungus infection was not suspected

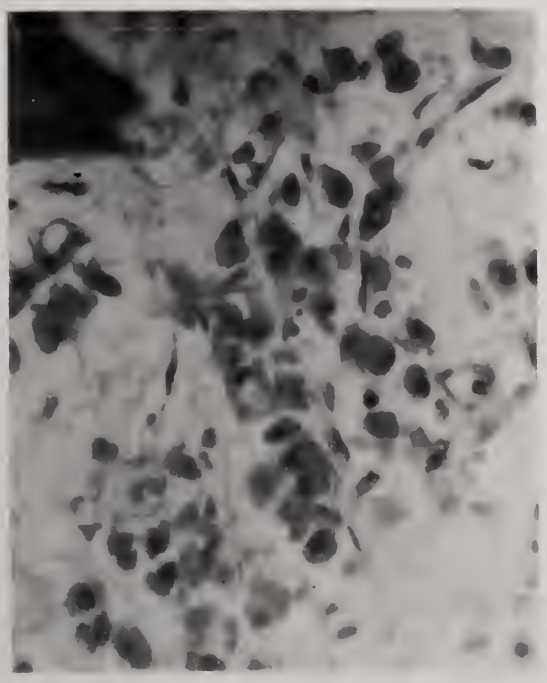


Fig. 3. Bone marrow H & E stain: Microphotograph shows clone of myeloma and plasma cells in a fibrillar matrix. Magnification X800.

at the time. The nature of the yeast phase of the fungus was identified by the H & E stained tissue sections of the pulmonary and regional tracheobronchial lymph nodes lesions. The fungus was clearly demonstrated by the PAS and Gomori's methenamine silver stains. Differentiation in tissue sections from *Histoplasma capsulatum* and *Blastomyces dermatidis* was established by the Mayer's reddish-pink mucicarmine staining of the polysaccharide capsule of the Cryptococcus fungus cells and a negative staining reaction in the other two fungi in reference. The latter are about the only fungi that would offer difficulty in a differential diagnosis in tissue sections. The positive carminogenic staining reaction of the capsule of the Cryptococcus cells is considered highly characteristic or specific as pointed out in the text Medical Mycology by Emmons, Binford and Utz (6).

Symmers (4) in his excellent paper on deep-seated fungal infections in England, makes reference to a historic case of cryptococcal mastitis in a 50-year old woman who had a mastectomy for a supposed colloid carcinoma of the breast. The above pathological facts should alert us pathologists in Puerto Rico where the existence of the fungus in the soil is very probable and as well its airborne pulmonary infections resulting in the more frequent healed fibrocaseous parenchymal nodules. This should stimulate us in the investigation of pulmonary nodules with a diagnosis of probable tuberculous lesions without the definitive demonstration of positive acid fast bacillus in the affected pulmonary tissue.

In this case of multiple myeloma treatment on his last admission with melphalan and corticosteroids possibly predisposed the patient to the disseminated Cryptococcus infection. Symmers (4) emphasized the role of drugs and other therapeutic measures as predisposing causes of deep-seated fungi infections in malignant diseases of reticuloendothelial system like lymphomas and leukemia. He made specific reference to a case of Hodgkin's disease treated with radiotherapy, corticosteroids and courses of various cytotoxic drugs and finally complicated by acute leukemia and multiple septicemic fungal infection and *Cryptococcus neoformans* pneumonia and meningitis. Zimmerman and Rappaport (3) in their paper concerning the occurrence of Cryptococcus infections in patients with malignant lymphoma or leukemia are usually disseminated, while those not associated are infrequently disseminated. They present evidence toward increased susceptibility of patients with Hodgkin's disease and allied disorders to certain infectious diseases including cryptococcosis.

The predisposition to the disseminated form

of the disease in association with cortisone has been shown experimentally by Levine *et al* (5) as already mentioned in the introduction of this paper. A poor inflammatory response to the Cryptococcus was also observed by us in the lungs and other organs. This was also supported by the lack of a tissue granulomatous reaction as an expression of poor tissue resistance. Melphalan is not known to have any imunosupressive action.

The serum protein electrophoresis in this patient showed a hypogamaglobulinemia with a value of 8.04 percent. Normality lies in the range of 16-18 percent. This phenomenon has been observed in studies in multiple myeloma by various methods of the determination immunoglobulins in this disease by Osserman and Tekatsui (7). It is also believed by these authors that marked susceptibility to bacterial infections presumably in large measure are due to marked deficiency in normal gamma globulin production. It may be postulated that a deficient production of normal gamma globulins by the neoplastic plasma cells existed in this case of disseminated cryptococcosis.

A negative urinary reaction for Bence-Jones proteins is not an uncommon finding in multiple myeloma. Lichtenstein and Jaffe found evidence of Bence-Jones protein in the urine in only 26 cases investigated by them (9). Menêndez-Corrada *et al* (8) found only 2 cases with Bence-Jones proteinuria among the 17 cases of multiple myeloma in their serum electrophoresis studies. Urinary electrophoresis studies were not carried out in the case under discussion and this fact does not allow us to expand on this subject; except to say that these are proteins of low molecular weight or microglobulins (7), products of degradation, of pathological gamma globulins.

Summary

A case of disseminated cryptococcosis in a patient with multiple myeloma under treatment with melphalan and prednisone has been presented. The pathology of the massive pulmonary and tracheobronchial lymph nodes infection has been described stressing the little tissue reaction to the fungus cells and the mucoid appearance of the lesions mimicking those of a Pseudomonas infection or even a colloid carcinoma. The usefulness of the PAS stain in a tissue diagnosis of the fungus has also been brought out in the discussion.

Resumen

Se presenta un caso de criptococcosis sistémica en asociación con mieloma múltiple bajo tratamiento con melphalan y prednisona. Se ha discutido la anatomía patológica de la infección masiva pulmonar y ganglios traqueobronquiales recalcando la apariencia mucoide de las lesiones, y la reacción tisular leve al hongo a veces simulando una neumonía a Pseudomonas o a un carcinoma mucoide del pulmón. Se ha enfatizado la necesidad de distinguir el criptococcus en la forma de levadura de hongos con morfología similar al *Histoplasma capsulatum* y *Blastomyces dermatides*, mediante la tinción carminogénica de la cápsula por el método de Mayer, PAS u otro similar.

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EDITORIALES

LA ESCUELA DE MEDICINA ANTE LA PLANIFICACION GLOBAL DE SALUD

La eficiente planificación global de salud es la tarea más importante a la que se enfrenta nuestro pueblo para lograr el objetivo de un Puerto Rico mejor. El éxito de todas las demás tareas tales como aquellas dirigidas a promover industrias, eliminar el desempleo y mejorar las condiciones de vida, está sujeto a que logremos llevar a toda la población la mejor calidad de medicina preventiva y curativa, y los mejores métodos de rehabilitación que permitan a todos gozar de vidas útiles y fructíferas (1).

La tarea de planificación global de salud entrega a los planificadores la difícil encomienda de planear con variables de tal magnitud que por necesidad tendrán que cometer errores. En la década del 70 esperamos que los adelantos científicos evolucionen a tal velocidad que nos enfrentarán a desarrollos imprevistos cuya aplicación será imposible planificar. Ante esta situación es imprescindible, en cualquier plan global de salud, proveer sistemas de gran flexibilidad para adaptarse a lo inesperado reconociendo la necesidad de dar la atención necesaria, a nuevos métodos de medicina preventiva, curativa y de rehabilitación.

Aunque no sea posible planificar en detalle los diferentes programas y servicios de salud futuros hay un aspecto de la planificación de salud que sin lugar a dudas necesita atención inmediata y fortalecimiento máximo. Este es el adiestramiento del personal médico y de colaboración médica que será indispensable para llevar a cabo la tarea que se planea (2). Si no le damos a este aspecto la primera prioridad estaremos planificando en un vacío. Necesitamos adiestrar un gran número de personas, pero números no serán suficientes; necesitaremos personas bien entrenadas cuya actitud, devoción y dedicación al trabajo sean extraordinarios.

Los nuevos adelantos de la medicina y nuevos programas de atención médica harán necesario, para responder a las necesidades que vislumbramos, un médico para cada 300 habitantes. También aumentará la necesidad de enfermeras, técnicos, y todo personal de colaboración médica. Si el aumento en este personal no va a la par con el aumento en médicos estos se verán con las manos atadas ya que gran parte de la prestación de servicios de salud en el futuro será función de equipos. El médico, salvo en algunas excepciones, tendrá que laborar en un ambiente de práctica de grupo en el cual colaborarán activamente con él enfermeras, terapistas, técnicos, y otro personal que, aún cuando esté llevando a cabo funciones especializadas, no lo hará en forma aislada sino uniendo sus esfuerzos a los del grupo por la mejor atención total del enfermo.

Para lograr tener suficiente número del personal de la salud y de la calidad que deseamos es necesario estimular la enseñanza de las ciencias biológicas en todo Puerto Rico y ampliar todas las actividades docentes en las ciencias de la salud, particularmente aquella del nivel universitario que por ley ha recibido esta encomienda: nuestro Recinto de Ciencias Médicas. El éxito de la enorme tarea que nuestros legisladores le han encomendado a nuestro Recinto de Ciencias Médicas dependerá de que se le provean facilidades adecuadas, personal suficiente, presupuestos adecuados, y estabilidad económica (3). En Puerto Rico las escuelas de Ciencias Médicas juegan un papel mucho más amplio en la solución de problemas de salud que el de la enseñanza, ya que además de su misión principal, cumplen otras cuyo impacto es decisivo sobre el éxito de los programas de salud de Puerto Rico.

La Escuela de Medicina está afectada por todos los aspectos relacionados con planificación global de salud. En nuestro ambiente más que en ningún otro conocido se le ha requerido participación directa en la salud de la comunidad y en la prestación de servicios a enfermos. Este tipo de actividad tiene la ventaja de crear un ambiente para enseñanza que ayuda a sensibilizar al estudiante hacia los problemas de la comunidad. Pero crea el peligro de que el compromiso de servicio por parte de la facultad sea tan grande que la actividad docente quede relegada a un plano secundario y se debilite la calidad de la enseñanza. La solución a este problema no debe consistir en retirar la Escuela de las actividades de servicio y aislarla en una torre de marfil. Más bien deberán proveérsele a la Escuela de Medicina las facilidades tanto para dar los servicios que merece el enfermo como para desarrollar el ambiente y efectuar cambios en los métodos de enseñanza que permitan educar al nuevo profesional necesario para la consecución de los planes globales de salud. Es imprescindible que estos profesionales se adiestren en un ambiente donde vivan y practiquen la atención total y eficiente del ser humano; de otra forma no sabrán de qué estamos hablando y no podrán llevar a la práctica la atención global de salud que estamos planeando. Para lograr este tipo de cuidado médico es indispensable el financiamiento adecuado de los hospitales-talleres de enseñanza. Las escuelas de Ciencias Médicas no podrán llevar a cabo su tarea docente en forma eficiente mientras se les coloque en la difícil posición de tener que utilizar sus recursos de enseñanza para resolver enormes problemas de servicios de salud. Aún cuando llevemos a cabo la tarea docente al precio más bajo posible, como lo está haciendo nuestra Escuela de Medicina, el costo de llevar a cabo enseñanza de alta calidad en las ciencias de la salud no puede bajar de un mínimo (4).

A pesar de las limitaciones existentes nuestra Escuela está respondiendo hasta el máximo de sus recursos a las necesidades de personal de salud de Puerto Rico aumentando su matrícula y mejorando la supervisión de los estudiantes. La clase graduanda del 1969 será la más grande en la historia de la Escuela hasta esa fecha, esperándose cerca de 60 graduandos, o sea, más de una docena sobre el promedio de los años anteriores. Mientras que este año todas las escuelas de medicina de Estados Unidos han aumentado la matrícula

de primer año en un promedio de dos estudiantes por escuela, la nuestra ha aumentado la matrícula en otros diez estudiantes para un total de 84 estudiantes en la clase entrante de agosto de 1968. Pensamos seguir aumentando la matrícula hasta llegar a 100 estudiantes por clase en el 1970 ó 1971. Para alcanzar estos objetivos nuestra Escuela necesitará toda la ayuda posible tanto de la clase médica como de la comunidad puertorriqueña, porque no es tarea del gobierno solamente. El éxito de nuestra Escuela de Medicina está ligado al de la planificación global de salud cuyo éxito es de todos y nos afecta a todos. Y este éxito depende de algo más que tener una fábrica de muchos médicos. Más bien depende de poder efectuar aumentos en matrícula, dentro de un ambiente educativo de excelencia que permita un mayor número de graduandos quienes a la vez sean excelentes, dedicados y compasivos profesionales conscientes de su responsabilidad total para con el paciente, su familia y la comunidad puertorriqueña.

José E. Sifontes, MD

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2. *Gerber, A.:* The medical manpower shortage. J. Med. Educ. 42: 306, 1967.
3. The crisis of the medical schools, a summary report based on the proceedings of the conference held in New York City, Sept. 15-17, 1967, sponsored by Carnegie Corp., N. Y., and Commonwealth Fund.
4. *Carroll, A. J. and Darley, W.:* Medical college costs. J. Med. Educ. 42: 1, 1967.

INICIACION

La confección de la comunicación formal escrita de los resultados de una investigación es una de las disciplinas esenciales en la formación del investigador médico. Esta requiere, además de la acumulación de data pertinente y de su interpretación, el dominio de las técnicas en el uso preciso del lenguaje. El entrenamiento en esta disciplina debe proceder paralelo a otras fases en la educación del médico joven.

En este número del Boletín, que dedicamos a los estudiantes de nuestra Escuela de Medicina, son varios de ellos los autores de los principales trabajos que aquí aparecen, y así se inician en el campo de la literatura médica. Esperamos establecer un precedente que sirva de estímulo a otros en el futuro.

Julio V. Rivera, MD

NOTA HISTORICA

Escuela de Medicina de Puerto Rico

José E. Sifontes, MD, Decano
Conrado Asenjo, PhD, Decano Asociado

El origen de la Escuela de Medicina de la Universidad de Puerto Rico se remonta al 1904 cuando el gobierno de Puerto Rico creó la Primera Comisión de Anemia luego del descubrimiento hecho por el Dr. Bailey K. Ashford sobre la relación existente entre uncinaria y anemia en Puerto Rico. El doctor Ashford, conjuntamente con los doctores Pedro Gutiérrez Igaravidez, Isaac González Martínez, Walter King, Agustín Stahl, Francisco Seín y otros, iniciaron por primera vez en la historia campañas de tratamiento de uncinaria en forma masiva, las que sirvieron de modelo para que se realizaran otras de igual índole fuera de Puerto Rico. En el 1912 se creó el Instituto de Medicina Tropical que continuó y amplió el trabajo de las Comisiones de Anemia iniciando trabajos importantes de investigación sobre sprue, uncinaria, filaria, esquistosomiasis y otras enfermedades tropicales. En el 1926 se convirtió el Instituto de Medicina Tropical en la Escuela de Medicina Tropical de la Universidad de Puerto Rico bajo los auspicios de la Universidad de Columbia y la misma fue dotada con un magnífico edificio estilo renacimiento español, el cual se amplió en el 1939 y en el 1947, respectivamente. La Escuela de Medicina Tropical ganó reconocimiento internacional por las investigaciones sobre enfermedades tropicales efectuadas en ella. En el 1948, por acuerdo mutuo, terminó la afiliación con la Universidad de Columbia y en mayo del siguiente año, por iniciativa del entonces Rector Don Jaime Benítez y sus asesores, se obtuvo acción legislativa para la creación de una Escuela de Medicina bajo el nombre oficial de Escuela de Medicina – Escuela de Medicina Tropical de la Universidad de Puerto Rico. Las facilidades académicas y físicas ya existentes en la vieja Escuela de Medicina Tropical fueron utilizadas para organizar y alojar las ciencias básicas y oficinas administrativas de la nueva Escuela, admitiéndose la primera clase en agosto de 1950. En la Fig. 1 aparece una gráfica que demuestra el número de admisiones, solicitud de admisiones y matrícula total al primer año de la Escuela de Medicina desde el 1950 hasta el presente. En el 1960 el Consejo Superior de Enseñanza le extendió su aprobación a los programas graduados de la Escuela de Medicina en los Departamentos de Anatomía, Bioquímica y Nutrición, Zoología Médica, Microbiología, Fisiología y Farmacología y más tarde en Patología. En el 1966, al aprobarse la nueva ley universitaria, la Escuela de Medicina pasó a formar parte del recién creado Recinto de Ciencias Médicas de la Universidad de Puerto Rico el cual quedó organizado bajo un rector, el anterior Decano de la Escuela de Medicina, Dr. Adán Nigaglioni, con su propio senado académico (véase Fig. 2) y junta administrativa. En la Fig. 3 aparece el organograma del nuevo Recinto.

La facultad de la Escuela de Medicina, que inicialmente estaba constituída por un número reducido de claustrales a jornada completa y un gran número de claustrales a jornada parcial y ad-honorem, ahora cuenta con un total de 328 claustrales de los cuales 227 son miembros de la facultad a jornada completa. En julio de 1968 fue aprobada la construcción del nuevo edificio de Ciencias Médicas por el gobierno federal con aportaciones universitarias y federales. En la Fig. 4 aparece la maqueta de lo que se proyecta será el nuevo edificio del Recinto de Ciencias Médicas, en el cual se alojarán las Escuelas de Medicina,

Fig. 1: Admisiones a la Escuela de Medicina y Proyecciones hasta 1970.

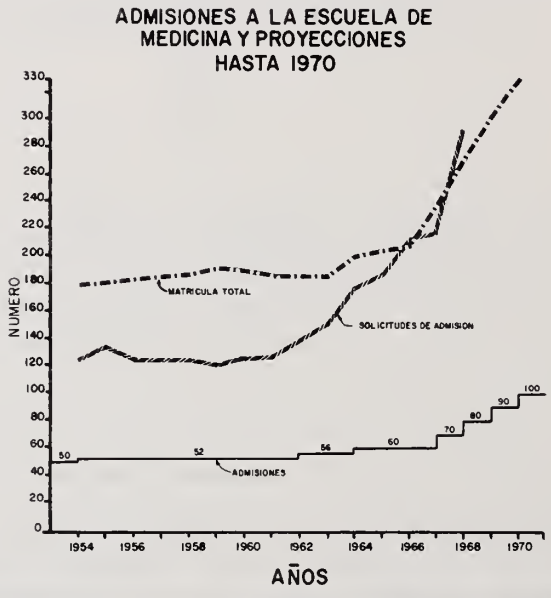




Fig. 2: PRIMER SENADO ACADEMICO DEL RECINTO DE CIENCIAS MEDICAS – 1966.
1) Dr. Mario García-Palmieri, 2) Dr. Francisco L. Raffucci, 3) Dr. Adán Nigaglioni, 4) Ledo. Jaime Benítez, 5) Sra. Lillian Casas de López, 6) Dr. Lowell E. Mckelvy, 7) Dr. Domingo Donate, 8) Dr. Rafael Mariñelarena, 9) Dr. José Oliver-González, 10) Dr. José Guillermo Frontera, 11) Dr. Walter Stiehl, 12) Dr. Juan E. Morales, 13) Dr. Renato Royo, 14) Dr. José E. Sifontes, 15) Dr. Arthur H. Schmidt, 16) Dr. Miguel Pastrana.

Fig. 3: Organograma del nuevo Recinto de Ciencias Médicas de la Universidad de Puerto Rico.

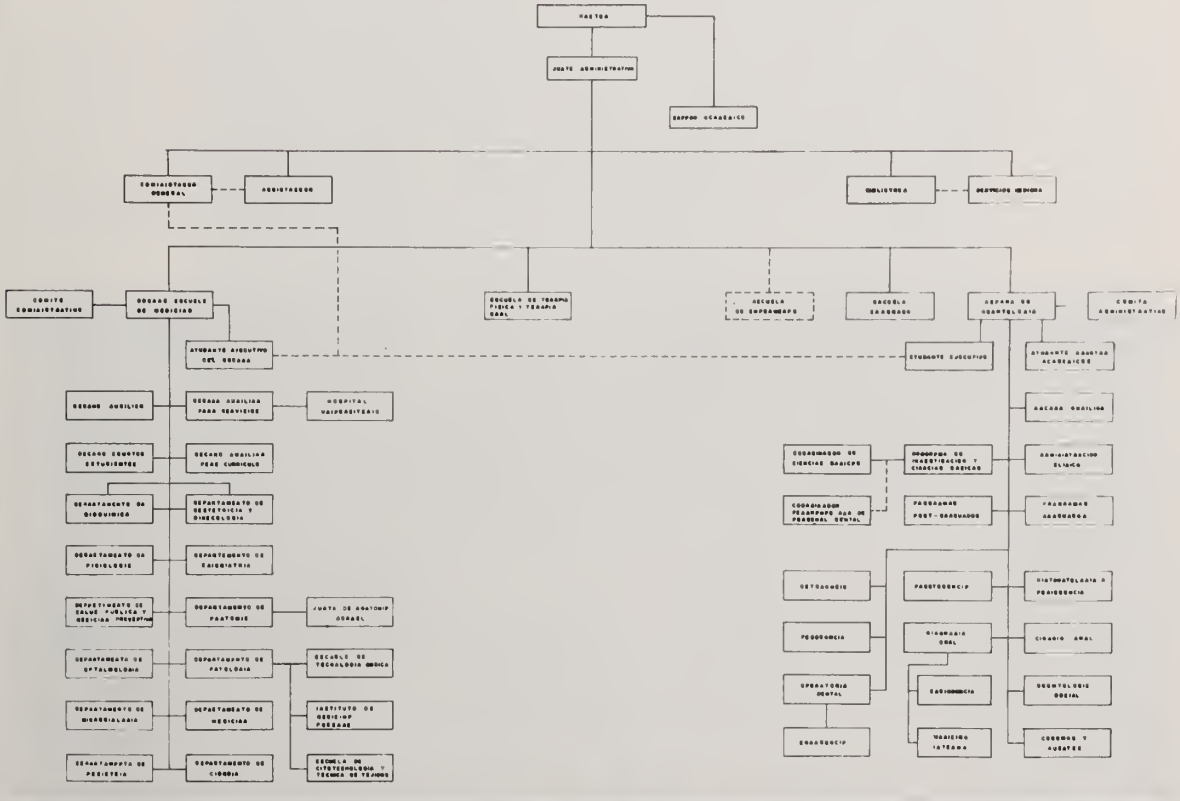




Fig. 4: Maqueta del edificio del Recinto de Ciencias Médicas.

Odontología y Salud Pública y las oficinas administrativas del Recinto de Ciencias Médicas. Además, tendrá un edificio adyacente para la nueva biblioteca del Recinto. Se espera que estas facilidades estén terminadas para fines de 1971.

Como record de gran importancia histórica se incluyen dos fotografías de la facultad de la Escuela. En la primera, Fig. 5, aparecen la mayoría de los profesores adscritos a los 2 primeros años de la Escuela de Medicina en el 1952, o sea, a los 2 años de haberse fundado. En la Fig. 6 aparece casi la totalidad de la facultad de las ciencias básicas y clínicas, dos años más tarde, o sea en el 1954. Al calce de todas las fotografías aparecen los nombres de las personas que se han podido identificar. Un número limitado de personas no se han podido identificar. Le agradeceremos a los que lean esta breve nota que, si reconocen a alguno de los que se nos escapan sus nombres, sean tan amables de informárnoslo.

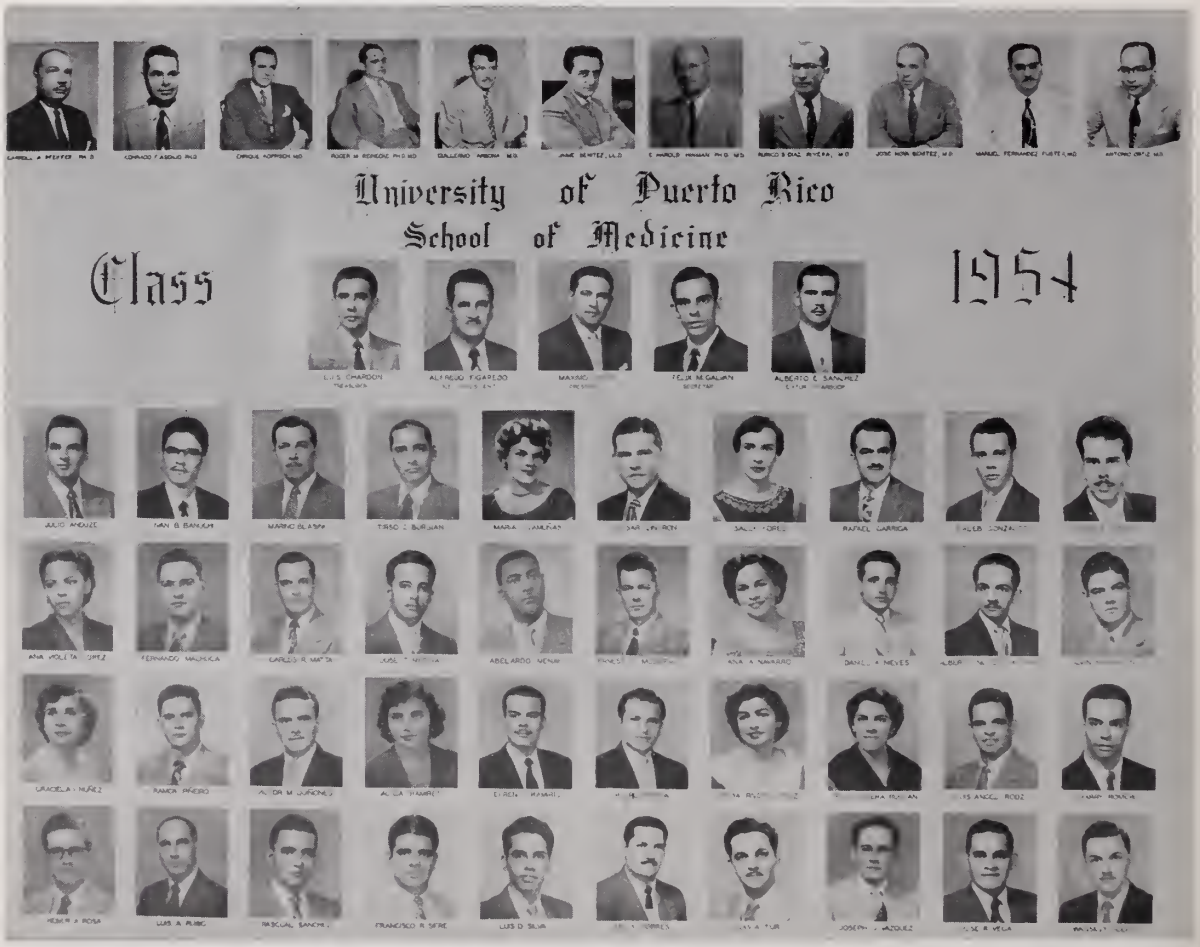


Fig. 5: PARTE DE LA FACULTAD DE LOS PRIMEROS DOS AÑOS DE LA ESCUELA DE MEDICINA – 1952. 1) Dr. Roger M. Reinecke, 2) Dr. Granvil C. Kyker, 3) Dr. Harold Brown, 4) Dr. Donald S. Martin, 5)Dr. Enrique Koppisch, 6) Dr. Gustave J. Noback, 7) Dr. Guillermo Arbona, 8) Srta. Josefina Acosta-Matienzo, 9) Dra. Blanca A. Lluberas, 10) Srta. Celia Guzmán, 11) Srta. Carmen Acevedo, 12) Dra. Eleanor Roverud Izquierdo, 13) Dr. Federico Diez Rivas, 14) Dra. Carmen Busó de Casas, 15) Srta. Diana A. Cameron, 16) Prof. José A. Goyco-Daubón, 17) Dr. Américo Pomales-Lebrón, 18) Dr. Luis M. González-Martínez, 19) Dr. Guillermo Ruiz Cestero, 20) Dr. José Noya Benítez, 21) Dr. Luis Adam-Nazario, 22) Dr. Ramón Ruiz-Nazario, 23) Dr. Conrado F. Asenjo, 24) Dr. Nelson Biaggi, 25) Dr. Walter M. Bond, 26) Dr. José Oliver-González, 27) Dr. José S. Licha, 28) Dr. Lorenzo Galindo-Merino, 29) Sr. José Luis Soto-Alarcón, 30) Dr. Hendrick Rijnders, 31) Sr. Rafael Pirazzi Rexach.



Fig. 6: GRUPO QUE INCLUYE PRACTICAMENTE TODA LA FACULTAD DE LOS DEPARTAMENTOS BASICOS Y CLINICOS DE LA ESCUELA DE MEDICINA – 1954. 1) ?, 2) Dra. Dharma Vargas, 3) Dra. Dolores Méndez-Cashion, 4) Dra. Marta Cancio, 5) Dra. Eloísa Muñoz, 6) Dra. Ydalia Ortiz, 7) Dr. Ismael Rodríguez-Bou, 8) Lcdo. Manuel Rodríguez-Ramos, 9) Lcdo. Manuel García-Cabrera, 10) Dr. José N. Gándara, 11) Lcdo. Jaime Benítez, 12) Dr.E. Harold Hinman, 13) Dr. José Noya Benítez, 14) Dr. Esteban García-Cabrera, 15) Dr. Alberto Mejía-Casals, 16) Dr. Fernando Batlle, 17) Dr. Juan Basora-Defilló, 18) Lcdo. Federico Tilén, 19) Dr. Antonio Ortiz, 20) Dr. Reinaldo A. Ferrer, 21) Dr. Manuel Astor, 22) Dr. Katherine Raresky de Rivera, 23) Dr. Julio V. Rivera, 24) Lcdo. Luis Torres-Díaz, 25) Dr. Guillermo Arbona, 26) Dr. José Chávez-Estrada, 27) Dr. Gladys Torres-Lamoutte, 28) Srta. Josefina Acosta-Matienzo, 29) Dr. Juan García-Esteve, 30) ?, 31) Dr. Guillermo Picó, 32) Dr. Rurico Díaz-Rivera, 33) Dr. José García-García, 34) Dr. Manuel Fernández-Fuster, 35) Dr. Antonio Navas-Torres, 36) Dr. Pedro Suau, 37) Dr. Ramón Sánchez-Viñas, 38) Dr. José A. de Jesús, 39) Dr. Orlando Bonilla-Soto, 40) Dr. Celso R. García, 41) Dr. Armando García-Castillo, 42) Dra. Edris Rice-Wray, 43) Dr. Jenaro Suárez, 44) Dr. Federico Diez-Rivas, 45) Dr. Rafael Gil, 46) Dr. Jaime Serra-Chavarry, 47) Dr. Juan Higinio Font, 48) Dr. Nelson Biaggi, 49) Dr. Luis A. Díaz-Bonnet, 50) Dr. Luis A. Passalacqua, 51) Dr. Manuel Guzmán-Rodríguez, 52) Dr. José Landrón-Becerra, 53) Dr. Carlos Guzmán-Acosta, 54) Dr. Lorenzo Galindo-Merino, 55) Dr. Robert King, 56) Dr. José Sárraga, 57) Dr. Jenaro Haddock-Suárez, 58) Dr. Dwight Santiago-Stevenson, 59) Dr. Carlos Muñoz-MacCormick, 60) Dr. José Picó, 61) Dr. Antonio Rullán, 62) Dr. Enrique Pérez-Santiago, 63) Dr. Luis Guzmán-López, 64) Dr. Raúl Marcial-Rojas, 65) Dr. Ernesto J. Marchand, 66) Dr. Ernesto Martínez, 67) Dr. Eugenio M. de Hostos, 68) Dr. José S. Licha, 69) Dr. Blas Ferraiouli, 70) Dr. Calixto Romero, 71) Dr. Héctor O. Hidalgo, 72) Dr. Elí Ramírez, 73) Dr. Luis Sanjurjo, 74) Dr. Alfred Axtmayer, 75) Dr. Francisco Berio, 76) Dr. Américo Pomales-Lebrón, 77) Dr. Juan M. Bertrán, 78) Dr. Néstor Méndez, 79) Dr. Pablo G. Curbelo, 80) Dr. Francisco Trilla, 81) Dr. Ariel Méndez, 82) Dr. Antonio Rivera-Trujillo, 83) Dr. José M. Torres-Gómez, 84) ?. 85) Dr. José Oliver-González, 86) ?, 87) Dr. Pablo L. Morales-Rodríguez, 88) Dr. José R. González-Giusti, 89) Dr. Andrés E. Salazar, 90) Dr. Rafael A. Vilar-Isern, 91) Dr. Rafael Mariñelarena, 92) Dr. Conrado F. Asenjo, 93) Dr. Carroll A. Pfeiffer, 94) Sr. Robert L. Dorsey, Jr., 95) Dr. Roberto J. Jiménez, 96) Dr. Walter A. Cervoni, 97) Dr. Juan A. Rosselló, 98) Dr. Juan E. Morales, 99) Dr. Herman Flax, 100) ?, 101) Dr. Henry Jeffay, 102) Dr. Roger M. Reinecke, 103) Dr. Antonio Ramos-Oller, 104) Dr. Francisco L. Raffucci, 105) Dr. Jaime Font-Casalduc, 106) Dr. Ernesto Colón-Jordán, 107) Dr. José Díaz-Carazo, 108) Sr. José A. Goyco-Daubón, 109) Dr. José F. Maldonado, 110) Dr. Carlos T. Armstrong-Ressy

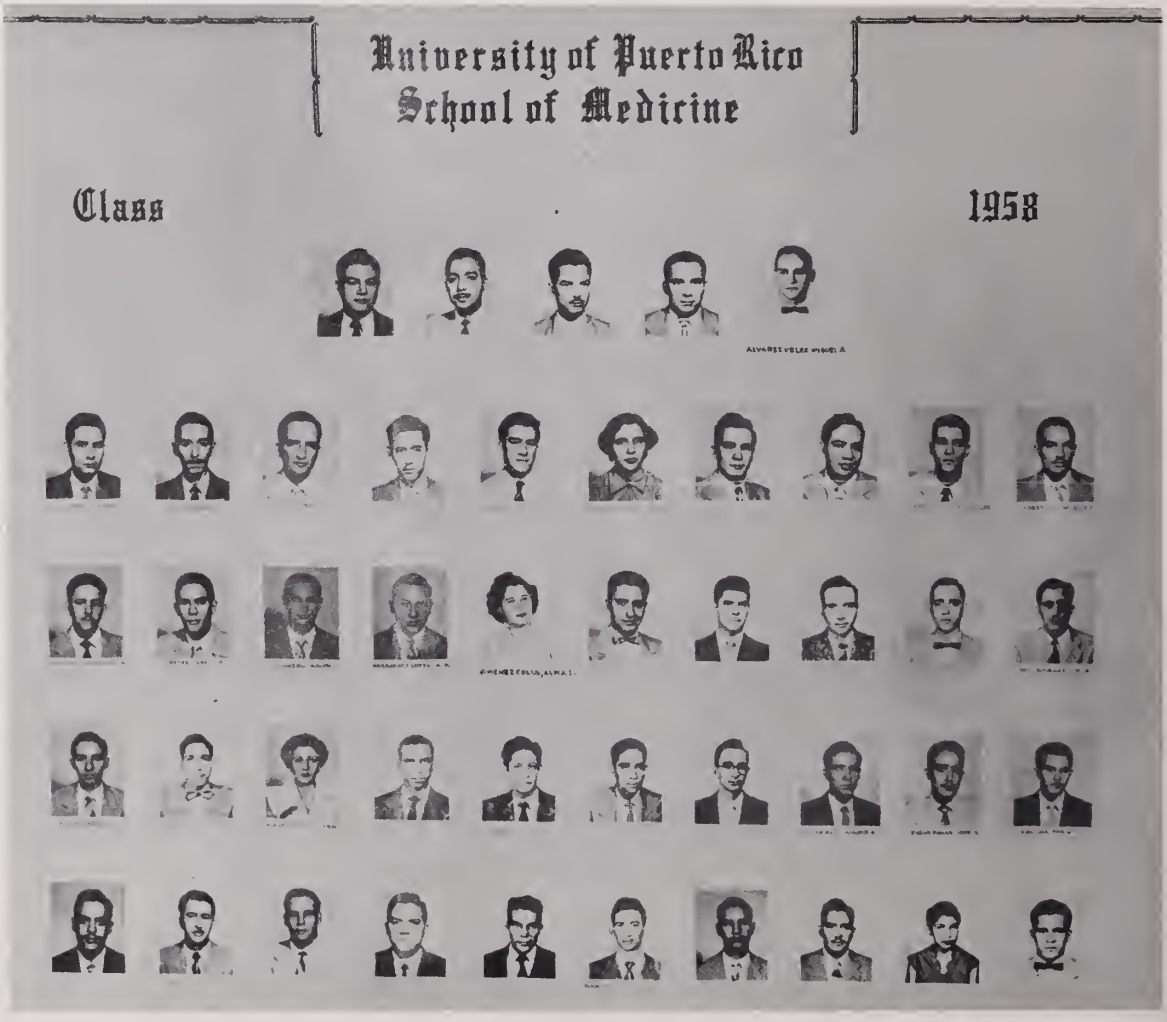
En las Figs. 7 a la 21 aparecen las fotografías de las 10 clases de graduados. Durante sus 18 años de existencia la Escuela de Medicina y sus varias dependencias y programas han graduado un total de 657 doctores en medicina, 3 doctores en filosofía (ciencias básicas), 20 maestros en ciencias (académicas), 984 maestros en varias áreas de la salud pública (profesionales), 202 bachilleres en terapia física y/o ocupacional, 165 bachilleres y certificados en tecnología médica, 278 bachilleres en enfermería, 48 certificados post graduados en records médicos, 50 certificados no graduados en salud pública y 6 certificados no graduados en terapia física y/o ocupacional para un gran total de 2,413 graduados a todos estos niveles.

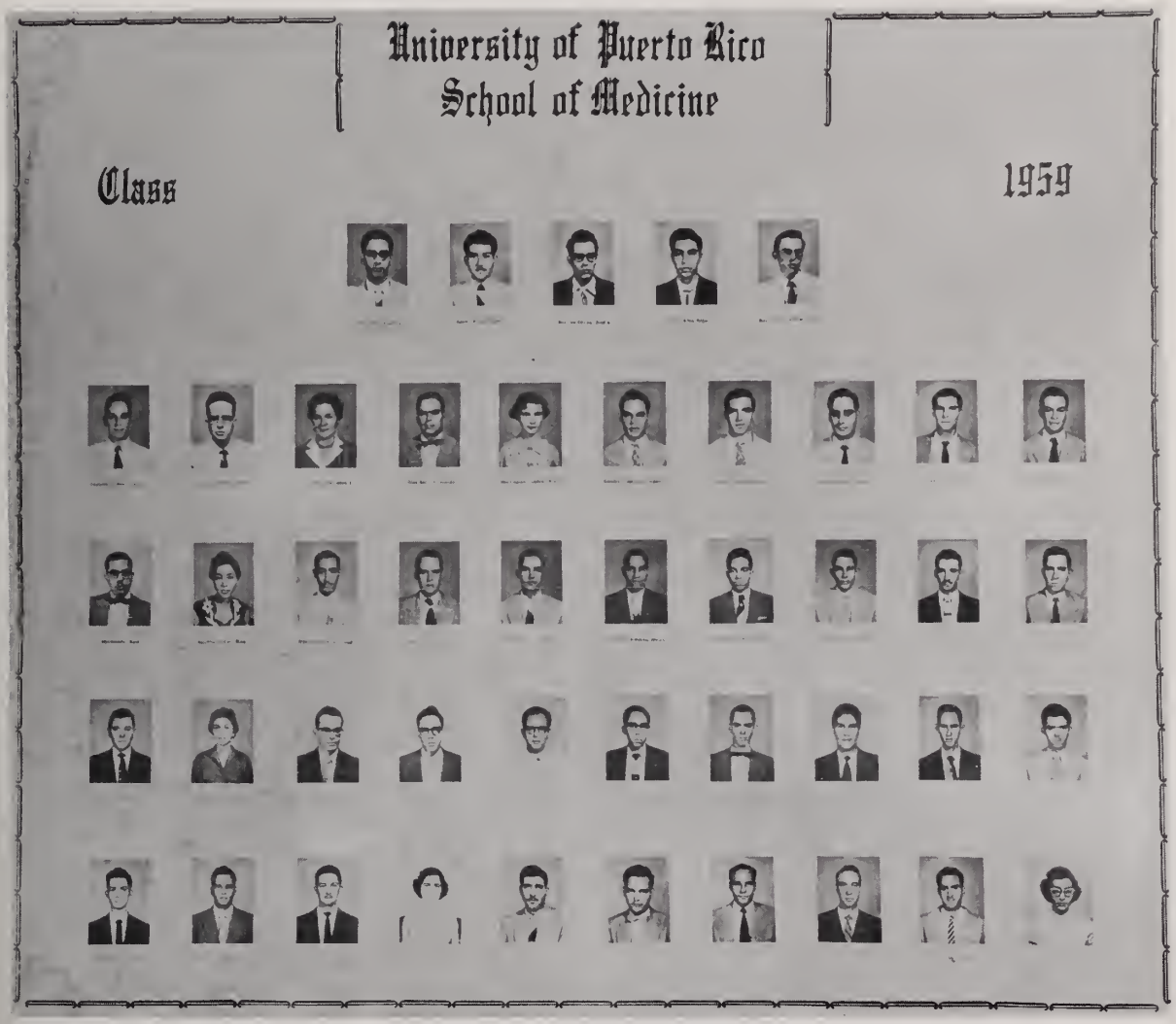



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BETSY CORDOVA
ENRIQUE M DE ARRIGOTTI
MYDA R DE JESUS
RAFAEL A DEL VALLE
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ARTURO MODESTO
HECTOR L MALEAC
VICTOR M PAGAN
JACINTO
GILBERTO ROSA
ARNALDO RIVERA
ANIBAL SEPULVEDA
GLORIA SOTOMAYOR
WALTER L STARK
JUAN J TUR
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ANGEL M VAZQUEZ
ENRIQUE V VELARDE
ALFONSO ZERBI

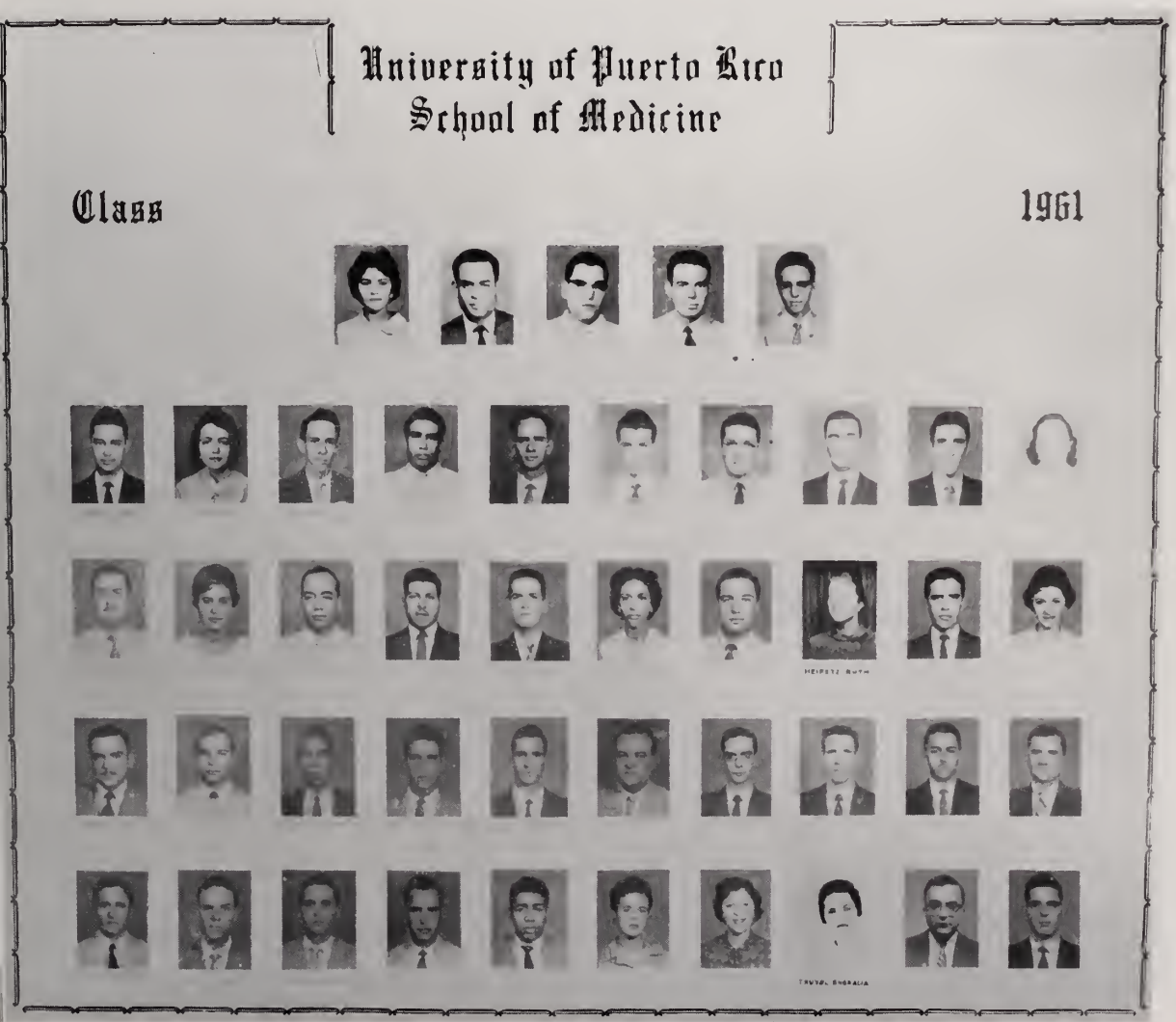

UNIVERSIDAD DE PUERTO RICO
Escuela de Medicina
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56


Escuela de Medicina
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Clase 1957
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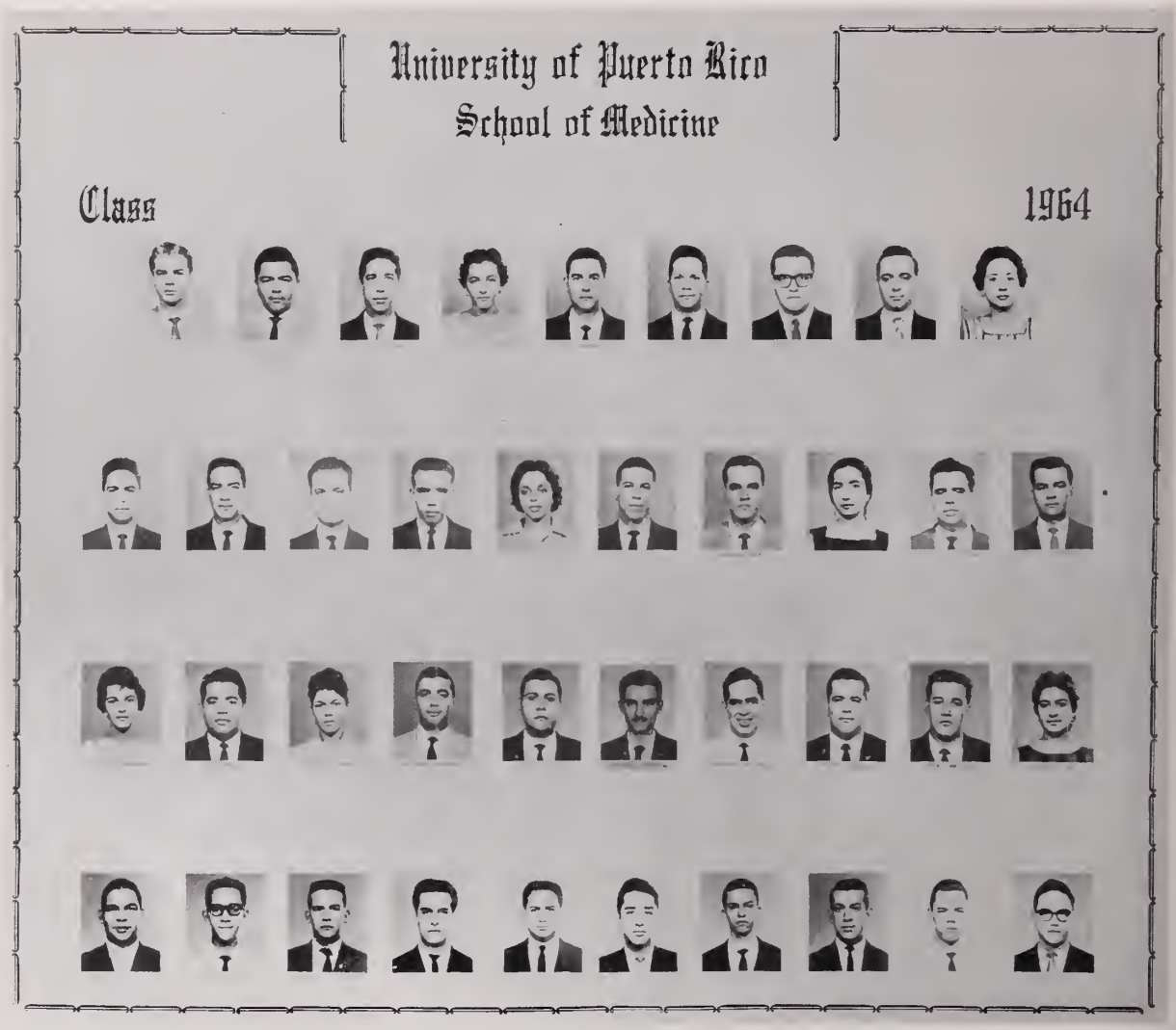

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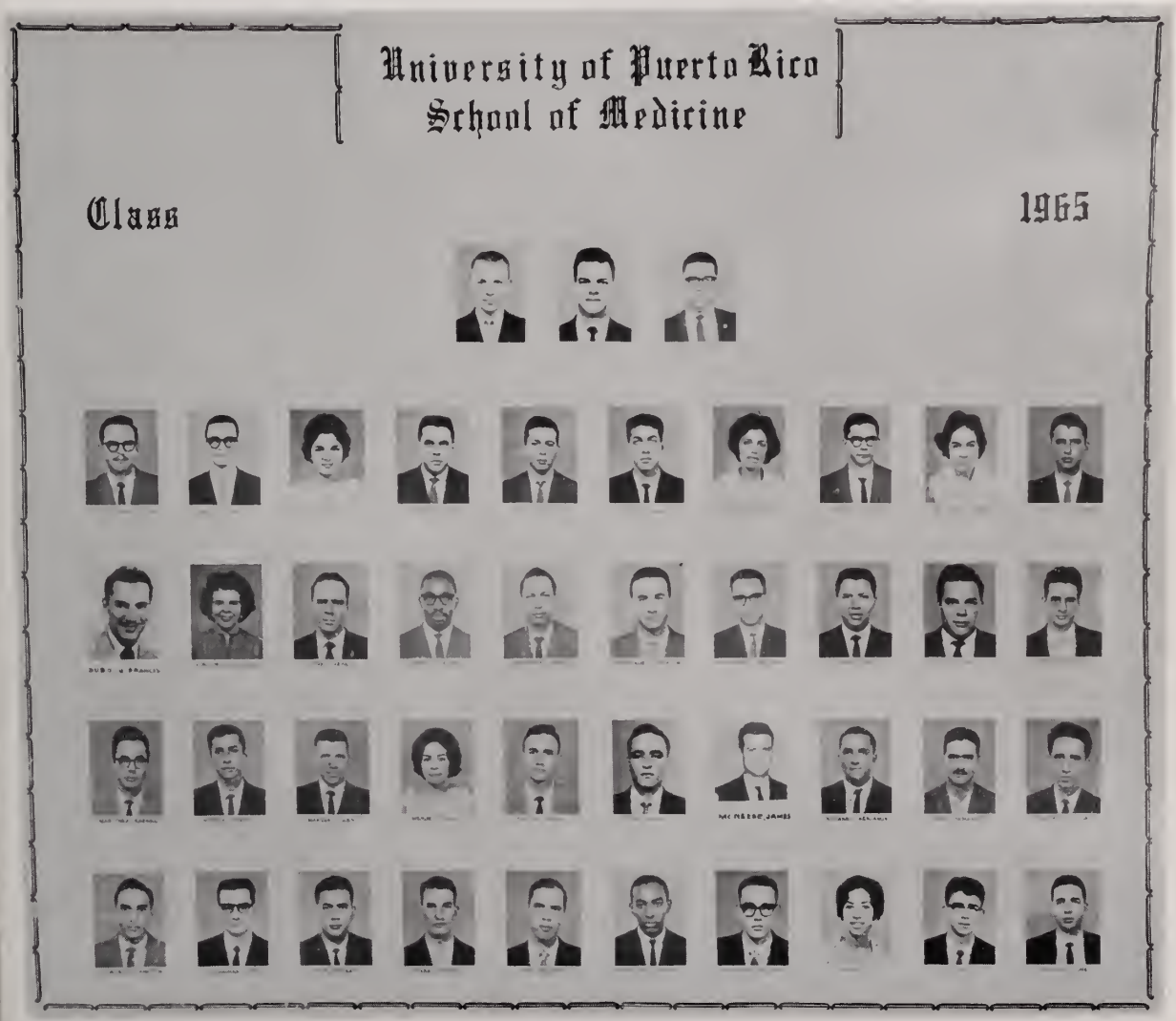

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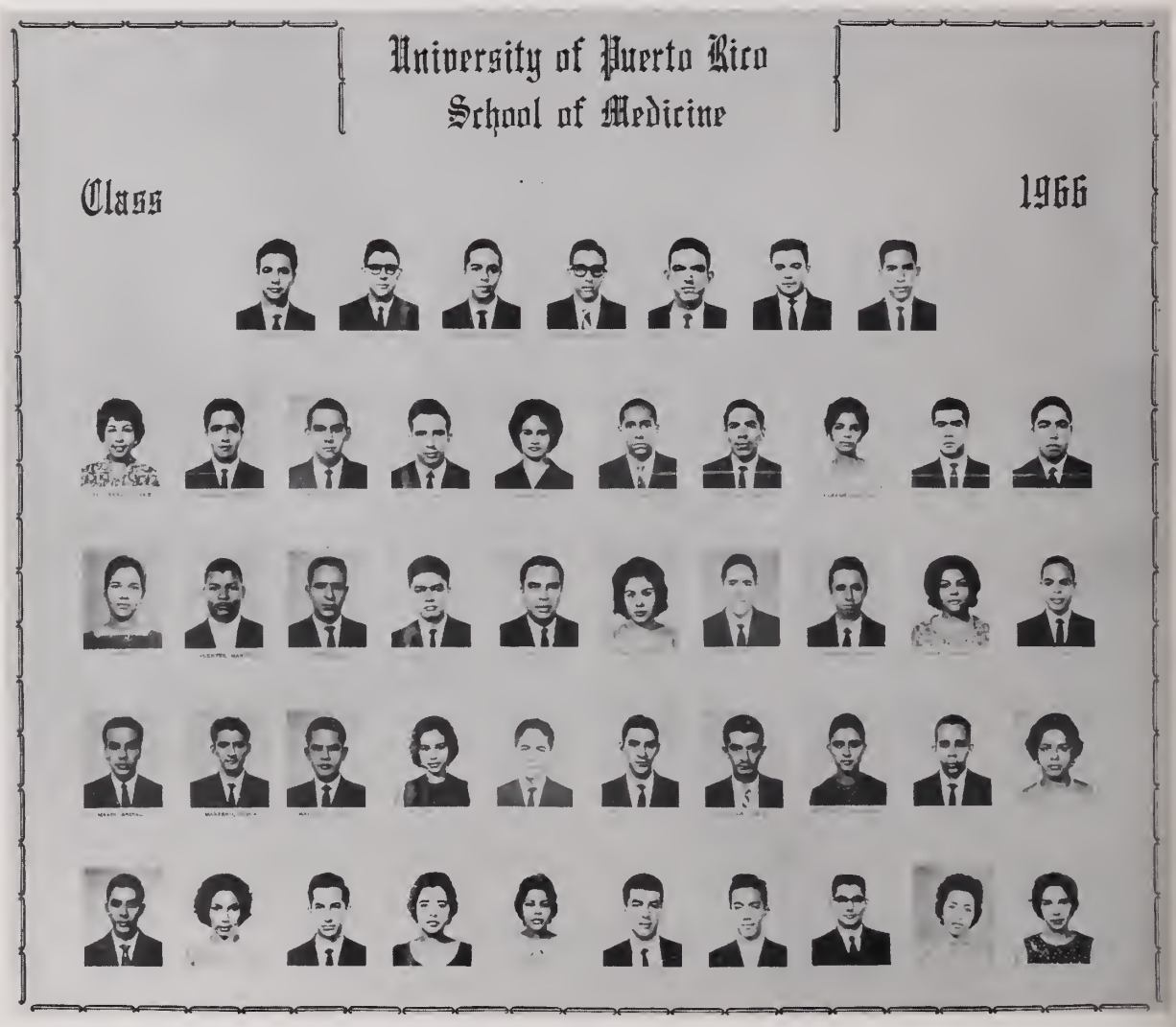

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1961

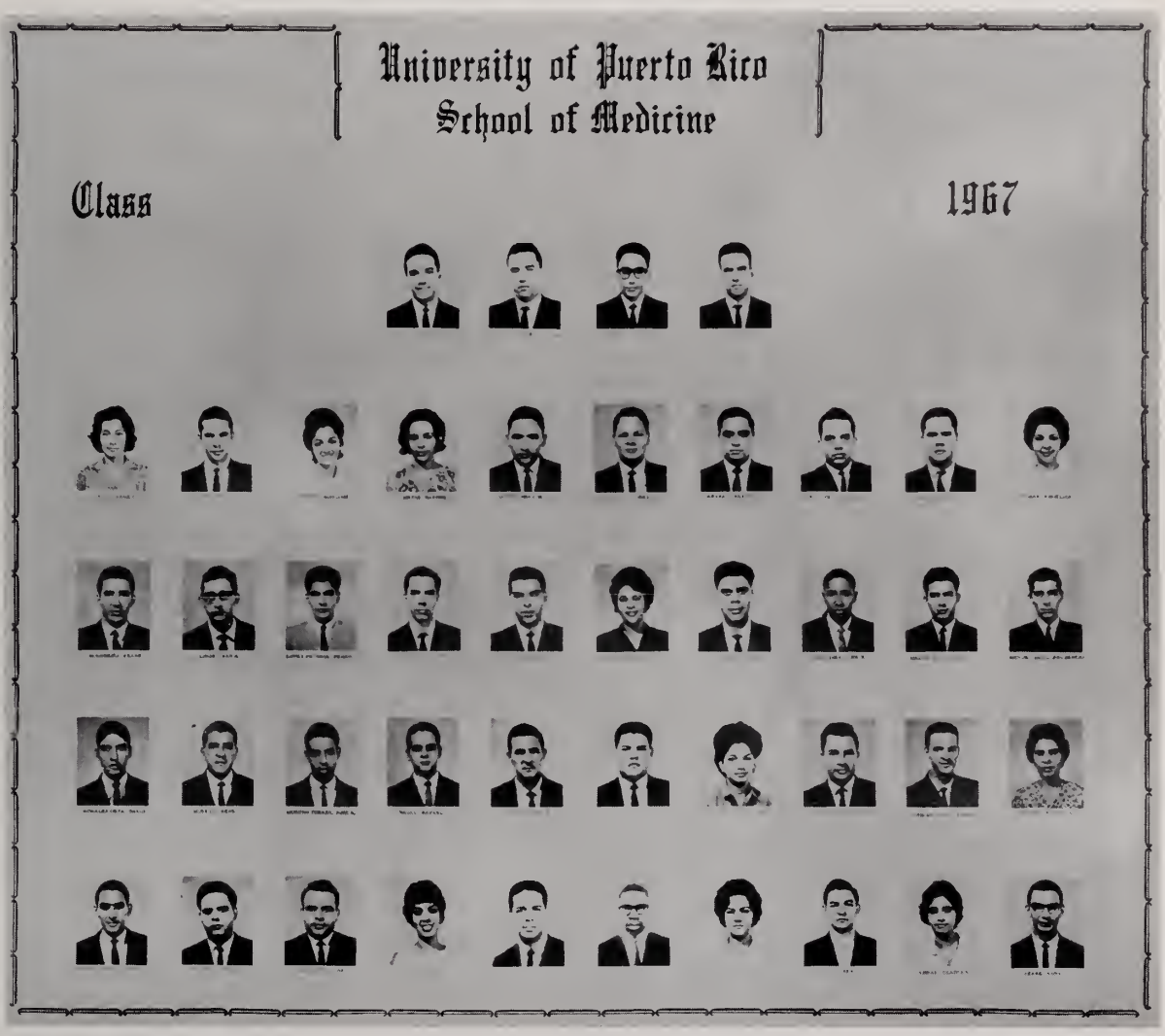

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1962

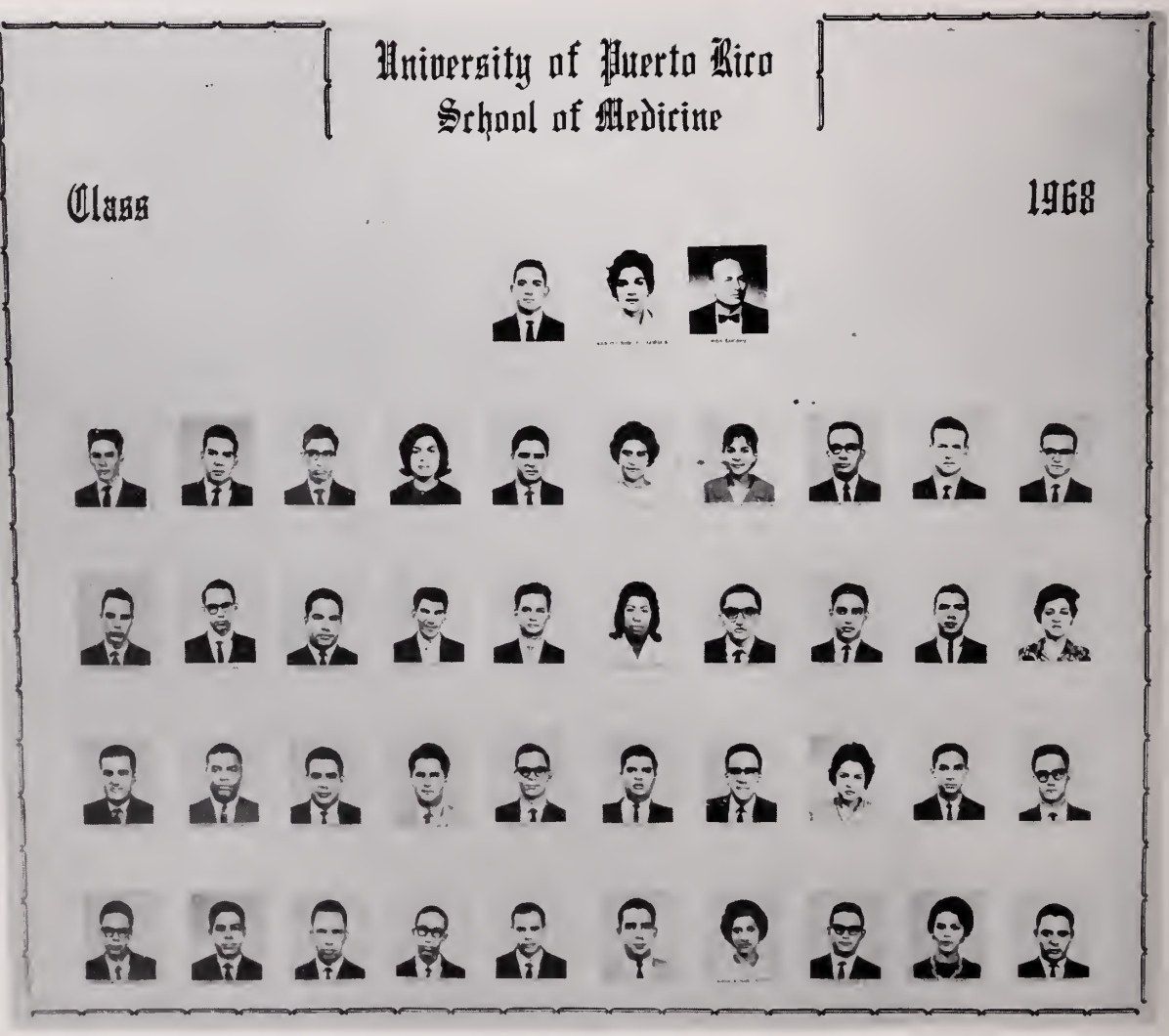

University of Puerto Rico
School of Medicine
Class
1963


University of Puerto Rico
School of Medicine
Class
1964


University of Puerto Rico
School of Medicine
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1965


University of Puerto Rico
School of Medicine
Class
1966


University of Puerto Rico
School of Medicine
Class
1967


University of Puerto Rico
School of Medicine
Class
1968

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

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ANUNCIOS

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Por motivos de estudio rento o vendo a médico generalista oficina equipada en sitio céntrico (Avenida Roosevelt 1129, Puerto Nuevo, Puerto Rico).

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In the complex picture of moderate to severe anxiety...



There is a **new** reason for prescribing Mellaril (Thioridazine HCl)

effectiveness in mixed anxiety-depression

Long recognized for its usefulness in the treatment of moderate to severe anxiety, Mellaril is now also known to be effective against mixed anxiety-depression.

Often the symptoms of anxiety states are difficult to sort out—even with the most careful probing. The patient may manifest symptoms of agitation, restlessness, insomnia, somatic complaints. But what of the depression that may be mixed in the total picture? It is reassuring to know that Mellaril may be prescribed—with strong possibilities of success—when there is anxiety alone or a mixture of anxiety and depression.

Before prescribing or administering, see Sandoz literature for full product information, including adverse reactions reported with phenothiazines. The following is a brief precautionary statement.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides. During pregnancy, administer only when necessary.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy may be avoided by remaining within the recommended limits of dosage. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving). Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension. Daily doses in excess of 300 mg. should be used only in severe neuropsychiatric conditions.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—Changes in the terminal portion of the electrocardiogram have been observed in some patients receiving the phenothiazine tranquilizers, including Mellaril (thioridazine hydrochloride). While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing electrocardiographic changes. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. *Other*—A single case described as parotid swelling.

Mellaril®
(Thioridazine HCl)
25 mg. t.i.d.

for moderate to severe anxiety and mixed anxiety-depression

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Louie lost weeks with acute shoulder bursitis. That's a l
of pain, stiffness and tenderness...and also a lot of fis
It might have been different with **Butazolidin® alk**

100 mg. phenylbutazone
100 mg. dried aluminum hydroxide gel
150 mg. magnesium trisilicate

If it doesn't work in a week, forget

But please don't forget this:

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently. Large doses of the alka formulation are contraindicated in glaucoma.

Warning: If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. Patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia); sudden weight gain (water retention); skin reactions; black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately before or after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to serum sickness may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.



Dosage in Painful Shoulder: Initial: 3 to 6 capsules daily in 3 or 4 equal doses. Trial period: 1 week. Maintenance dosage should not exceed 4 capsules daily; response is often achieved with 1 or 2 capsules daily.

In selecting the appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

(B) 46-070-B

For complete details,
please see full prescribing information.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York 10502

Butazolidin® alka Geigy

Capsules
100 mg. phenylbutazone
100 mg. dried aluminum hydroxide gel
150 mg. magnesium trisilicate

The Divorced Depressive: "Forty, Forgotten

"Had a large wedding."
"Had a fine home and family."



TO-5757

.Forlorn"

.d a divorce."
a real loser,
d so are
kids."



The loss of marital compatibility results in nearly 500,000 U.S. divorces each year.

Depression characterized by untold guilt feelings, grief and loneliness may follow.

When you diagnose depression, Tofrānil may be indicated for relief.

As maintenance therapy during the active phase of depression, Tofrānil can often help prevent relapse.

The use of Tofrānil in patients receiving M.A.O.I.'s is contraindicated. In patients with cardiovascular disease, thyroid disorders, increased intraocular pressure; in those receiving anticholinergics (including antiparkinsonism agents), thyroid medication or antihypertensive adrenergic neuron-blocking agents; and in those in their first trimester of pregnancy–the special precautions listed in the Prescribing Information should be carefully observed.

Toxic reactions severe enough to require discontinuation of Tofrānil are uncommon. However, for complete details, please refer to the complete Prescribing Information.

Turn page for brief summary of Prescribing Information.

in depression

Tofrānil® imipramine hydrochloride
Geigy

in depression





Tofrānil® Geigy

imipramine
hydrochloride

Tofrānil®, imipramine hydrochloride
Indications: Tofrānil is recommended for the treatment of depressive states of diverse psychopathology.
Contraindications: The concomitant use of this agent and monoamine oxidase inhibiting (M.A.O.I.) compounds is contraindicated. Hyperpyretic crises or severe convulsive seizures may occur. Potentiation of adverse effects can be serious or even fatal. An interval of at least 7 days after M.A.O.I. therapy has been discontinued should be allowed before this drug may be substituted. Initial dosage should be low, increases should be gradual, and the patient's progress should be carefully observed.
Warning: Clinical reports have suggested that there may be a risk of teratogenesis associated with the use of this compound during the first trimester of pregnancy. Unless, in the opinion of the prescribing physician, the potential benefits outweigh the possible risks, it should not be used during the first trimester of pregnancy.
Cardiovascular complications, including myocardial infarction and arrhythmias, have occasionally occurred in susceptible individuals. Patients with cardiovascular disease should be given the drug only under careful observation and in low dosage.
Precautions: Since suicide is always a possibility in severely depressed patients and one which may persist until significant remission occurs, such patients should be carefully supervised during early treatment. Some severely depressed patients may also require hospitalization and/or concomitant electroconvulsive therapy.
Because of its anticholinergic effect, caution should be observed in prescribing the drug for patients with increased intraocular pressure.
In rare instances, transient cardiac arrhythmias have occurred in hyperthyroid patients and in patients receiving thyroid medication when this compound was added to the regimen. Imipramine may block the pharmacologic activity of guanethidine and other related adrenergic neuron-blocking agents.
The drug is not recommended at the present time in patients under 12 years of age.
Adverse Reactions: Dryness of the mouth, tachycardia, constipation, disturbances of accommodation, sweating, dizziness, weight gain, urinary frequency or retention, nausea and vomiting, peripheral neuritis, mild parkinson-like syndrome, tremors, rare cases of falling in elderly patients, confusional states (with such symptoms as hallucinations and disorientation), activation of psychosis in schizophrenics and agitation (including hypomanic and manic episodes) which may require dosage reduction and/or addition of a tranquilizer or temporary discontinuation of the drug, epileptiform seizures, orthostatic hypotension and substantial blood pressure fall in hypertensive patients, purpura, transient jaundice, bone marrow depression including agranulocytosis, sensitization and skin rash including photosensitization, eosinophilia, and mild withdrawal symptoms on sudden discontinuation after prolonged treatment with high doses.
Occasional hormonal effects (impotence, decreased libido, and estrogenic effects) may be observed.
Atropine-like effects may be more pronounced (e.g. paralytic ileus) in susceptible patients and in those using anticholinergic agents (including antiparkinsonism drugs).
Outpatient Adult Dosage: Initially, 75 mg. daily, increased, if necessary, to 150 or 200 mg. Maintenance dosage may be lower, 50 to 150 mg. daily, if possible.
Geriatric and Adolescent Dosage: Initially, 30 or 40 mg. daily, which may be increased according to response and tolerance. It is usually unnecessary to exceed 100 mg. daily.
A lag in therapeutic response, lasting from a few days to a few weeks, should be expected. When dosage recommendations are already being followed, increasing the dosage does not normally shorten this latency period and may increase the incidence of adverse reactions.
Availability: Round tablets of 25 and 50 mg.; triangular tablets of 10 mg. for geriatric and adolescent use; and ampuls, each containing 25 mg. in 2 cc. for I.M. administration.
(B)R-46-850-C

For complete details, please refer to the full Prescribing Information.

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Ardsley, New York 10502

TO-6757

IN PATIENT BENEFITS

what does CHYMORAL's faster action mean? It can mean:

- Edema and inflammation subside twice as fast—healing time cut in half.
- The patient is restored to normal activities twice as fast.
- Lesions heal in less time—and the physical appearance of the patient improves twice as fast.
- Hospital stay...convalescent period...medication costs may be cut in half.

The benefits of CHYMORAL cover many conditions and the results[1] are worthy of mention.



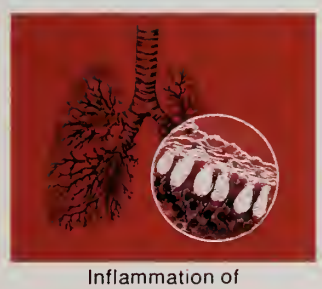
Surgical trauma

4123 cases **91%** had good/excellent results

3470 cases **89%** had good/excellent results



Episiotomy and pelvic inflammation



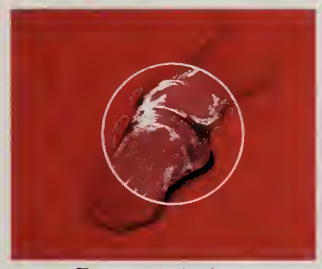
Inflammation of respiratory tract

2389 cases **80%** had good/excellent results

1055 cases **75%** had good/excellent results



Inflammatory dermatoses



Traumatic lesions

6929 cases **93%** had good/excellent results

2645 cases **83%** had good/excellent results

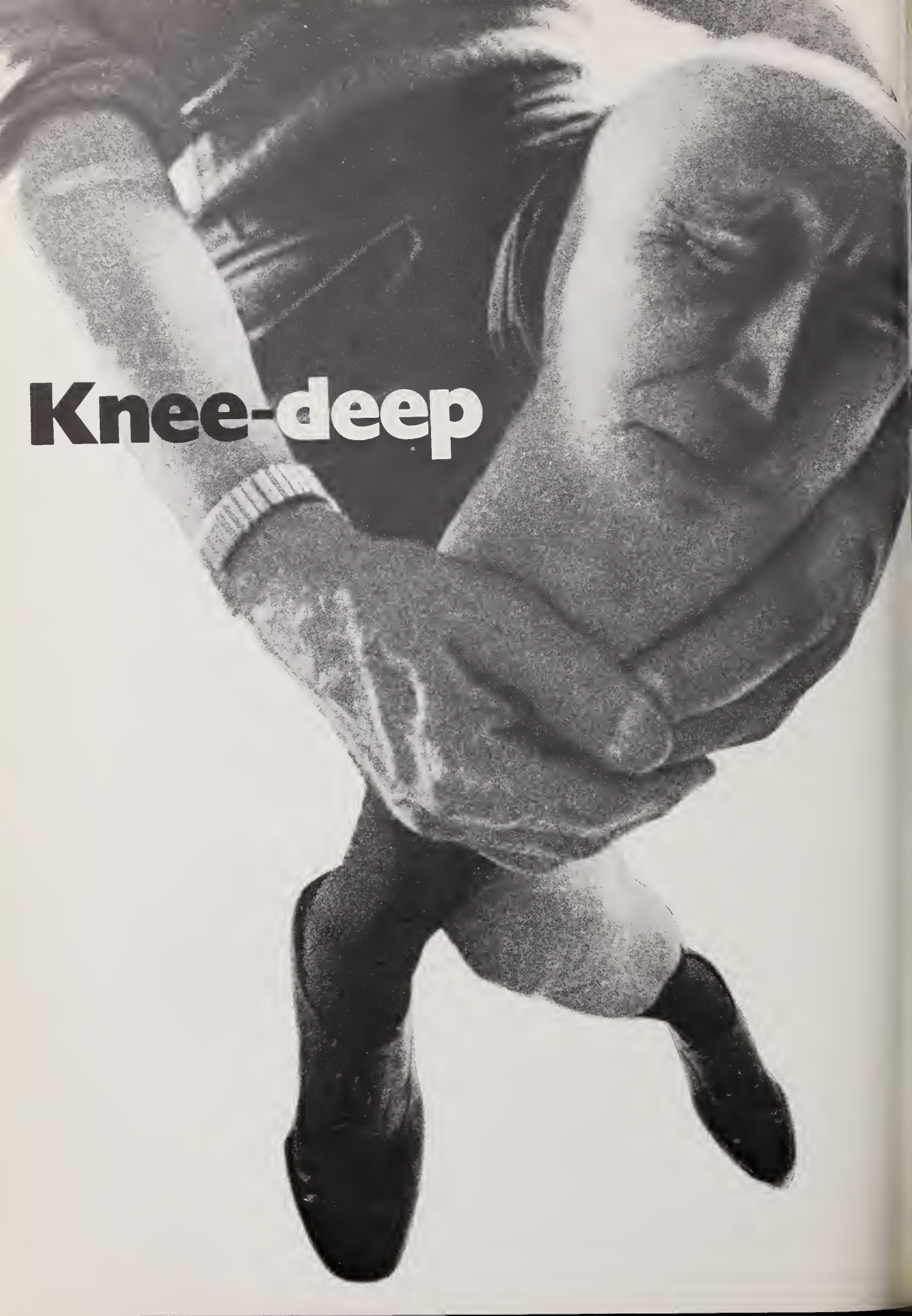


Eye, ear, nose and throat inflammations

***Rx.* CHYMORAL®—Enzyme tablets**

ARMOUR PHARMACEUTICAL COMPANY, Chicago, Illinois 60690, U.S.A.

[1]Based on clinical reports compiled by the Medical Division of Armour Pharmaceutical Company


Knee-deep

in osteoarthritic pain

If aspirin doesn't help, move in ith Tandearil.

The trial period is brief: 1 week. ry one tablet q.i.d. at first. Tandearil sually starts working within 3 to 4 days. When response occurs, as little as 1 or tablets daily may hold back pain and iffness, and increase joint motion.

On the next page is a summary adverse reactions, contraindications, arning and precautions.

Tandearil.
It can help get his mind off his knee.

Please review full Prescribing Information carefully before prescribing.

For osteoarthritic knees, spines, shoulders, hips, etc.:

Tandearil®
oxyphenbutazone

Tandearil, oxyphenbutazone:
For brief summary see next page.

Geigy



Tandearil®
oxyphenbutazone

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily.

In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

(B)R-46-800-A

For complete details, please see full Prescribing Information.

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Division of
Geigy Chemical Corporation
Ardsley, New York 10502



para esa tos molesta recomiende el nuevo jarabe, sin narcóticos

Cheracol D

dominio efectivo de la tos, sin codeína

Cheracol D con dextrometorfano:

- acción antitusiva igual que con codeína, pero sin efectos secundarios narcóticos indeseables
- afloja las secreciones bronquiales
- refresca y suaviza la garganta
- tiene un agradable sabor a cerezas que lo hace muy popular entre los niños
- puede ser administrado a niños menores de dos años, bajo la vigilancia del médico

Cada onza fluida contiene:

Bromhidrato de dextrometorfano	9/10 gr. (60 mg.)
Cloroformo*	2 grs.
Guayacolato de Glicerilo	1⅖ grs.
Cloruro de Amonio	8 grs.
Tartrato de Antimonio y Potasio	1/12 gr.
Alcohol	3%

con corteza de pino blanco y de cerezo silvestre

*Cierta pérdida de cloroformo es inevitable.

Presentación: en frascos de 2 y 4 onzas.

Upjohn

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Whenever anxiety induces or intensifies clinical symptoms

Librium®

(chlordiazepoxide HCl)

Quickly relieves anxiety~Helps improve response in psychophysiologic disorders~Seldom impairs mental acuity or physical coordination, on proper dosage~ Has wide margin of safety

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Indicated when anxiety, tension and apprehension are significant components of the clinical profile.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral*—Adults: Mild and moderate anxiety and tension, 5 or 10 mg t.i.d. or q.i.d.; severe states, 20 or 25 mg t.i.d. or q.i.d. Geriatric patients: 5 mg b.i.d. to q.i.d. (See Precautions.)

Supplied: Librium® (chlordiazepoxide HCl) Capsules, 5 mg, 10 mg and 25 mg—bottles of 50. Libritabs™ (chlordiazepoxide) Tablets, 5 mg, 10 mg and 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

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BOSTON
31 MAR 1969

VOL. 60 DICIEMBRE, 1968 NUM. 12

Why DBI-TD (phenformin HCl) is the only significant advance in oral diabetes therapy since sulfonylureas



□ glucose ○ insulin

1 Only DBI-TD does more than just lower blood sugar–it directs sugar primarily to where it is most needed... in muscle.

In the maturity-onset diabetic, blood sugar is elevated, but apparently not enough glucose enters muscle. Unlike other agents, DBI-TD increases glucose utilization primarily in skeletal muscle where sugar is needed.

2 Only DBI-TD actually promotes weight loss in the maturity-onset diabetic who is overweight.

All oral drugs *except* DBI-TD increase insulin release, which suppresses lipolysis and can accelerate lipogenesis. Thus DBI-TD, by avoiding insulin oversecretion, appears to ease—rather than aggravate—the weight problem in patients unresponsive to diet alone.

3 Only DBI-TD, among oral agents, helps counterbalance the inefficient action of the diabetic's own insulin.

There is increasing evidence that many overweight maturity-onset diabetics have higher than normal blood insulin levels, but this insulin is not efficient in promoting muscle glucose uptake. Unlike all other oral agents, DBI-TD helps control diabetes by selectively moving sugar into muscle without further increasing insulin levels.

4 Only DBI-TD, because of its unique action, reduces the risk of secondary failure and hypoglycemic reaction.

DBI-TD is the only agent that lowers blood sugar without stimulating the release of insulin from the pancreas. Secondary failures are infrequent with DBI-TD, and there is relative freedom from hypoglycemic reaction when DBI-TD is used alone.

a more physiological approach to begin with

DBI®-TD

(phenformin HCl)

timed-disintegration capsules 50 mg.

Dosage: 1 to 3 capsules daily. **Side Effects:** Gastrointestinal, occurring more often at higher dosage levels, abate promptly upon dosage reduction or temporary withdrawal. **Adverse Reaction:** Urticaria. **Precautions:** Occasionally an insulin-dependent patient will show "starvation" ketosis (acetonuria without hyperglycemia) which must be differentiated from "insulin lack" ketosis which is accompanied by acidosis, and treated accordingly. Lactic acidosis has been reported in nondiabetics and diabetics treated with insulin, with diet, and with DBI. Question has arisen regarding possible contribution of DBI to lactic acidosis in patients with renal impairment and azotemia and also those with severe hypotension secondary to myocardial or bowel infarction. Periodic B.U.N. determination should be made when DBI is administered in the presence of chronic renal disease. DBI should not be used when there is significant azotemia. Any cardiovascular lesion that could result in severe or sustained hypotension, which may itself lead to development of lactic acidosis, should be considered cause for immediate discontinuation of DBI at least until normal blood pressure has been restored and is maintained without vasopressors. Should lactic acidosis occur from any cause, vigorous attempts should be made to correct circulatory collapse, tissue hypoxia, and pH. **Contraindications:** Severe hepatic disease, renal disease with uremia, cardiovascular collapse. Not recommended without insulin in acute complications of diabetes (metabolic acidosis, coma, severe infections, gangrene, surgery). ***Pregnancy Warning:*** *During pregnancy, until safety is proved, use of DBI, like other oral hypoglycemic drugs, is to be avoided.* **Also Available:** DBI tablets 25 mg. *Consult product brochure.*

USV

USV PHARMACEUTICAL CORP., New York, N.Y. 10017
Producers of ARLIDIN® (nylidrin HCl)

A dilemma of the aged



Whitman's malady. In 1858, three years after publishing *Leaves of Grass*, Walt Whitman suffered "a mild seizure and he recovered so rapidly that he always thought it was sunstroke."[1] From then on his life was a succession of similar events—'silent' strokes—punctuated by big strokes. In between, "... spells of fainting and very bad feeling in my head, fullness and pain ... bad spells, dizziness in the head."[2]

Were Whitman's prodromal episodes transient cerebral ischemia—resulting from vasospasm? Who can know for sure? The great Osler's initial observation of the poet was: "...There was nothing serious the matter—a transient indisposition which had passed away..."[2] A Dr. Grier said Whitman's "real disease is the brain not being properly furnished and nourished with blood..."[2] And there has been a long-held view that the instantaneous onset of such episodes, and their rapid disappearance without apparent residue, are compatible with a concept of cerebral vasospasm.

1. Page, I.H., *et al.*: Strokes, New York, Dutton, 1961, p. 11. 2. Feinberg, C.E.: Arch. Intern. Med. *114*:834, Dec. 1964.

transient cerebral ischemia
(due to vasospasm)

Patients often awake with a headache, memory loss, dizziness or confusion

Although transient cerebral ischemia may develop at any time, it often occurs at night. Its victims may awake the next day dizzy and confused, or temporarily incapacitated. A cerebral vasodilator may help relieve the ischemic syndrome due to arterial spasm. But if vasodilation is to provide adequate protection against recurrent episodes, it must maintain vital blood flow even while the patient sleeps.

Cerespan q.12 h. helps protect the patient— even while he sleeps

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Each Cerespan capsule contains papaverine HCl 150 mg. in micro-dialysis cells. Class M Narcotic. **Indications and Dosage:** For relief of cerebral and peripheral ischemia associated with spasm, 1 capsule *q.12 h.* **Precaution:** Use with caution in glaucoma. **Side Effects:** Rare; those reported include anorexia, nausea, abdominal distress, constipation, malaise, drowsiness, vertigo, sweating and headache.

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(PAPAVERINE HCl) q.12 h.

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Los pacientes obstétricos o post-quirúrgicos que requieren un método seguro para elevar su hemoglobina, recibirán tanto hierro (250 mg.) de una inyección de 5 c.c. de IMFERON como el que contiene una pinta (500 c.c.) de sangre fresca. El IMFERON (inyección de hierro dextrán) es menos costoso y evita los bien conocidos peligros que entraña la transfusión de sangre total. En los pacientes que no pueden tomar hierro o en aquellos en quienes no se puede confiar que lo hagan, el IMFERON (inyección de hierro dextrán) suministra rápidamente el hierro necesario para los depósitos de reserva.

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QUE UNA AMPULA DE 5 cc. DE



IMFERON

(inyeccion de hierro dextran)

LAKESIDE LABORATORIES, INC.
Milwaukee, Wisconsin 53201, U.S.A.

LAKESIDE

PRODUCTOS PARA PACIENTES QUE UD. VE A DIARIO

RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

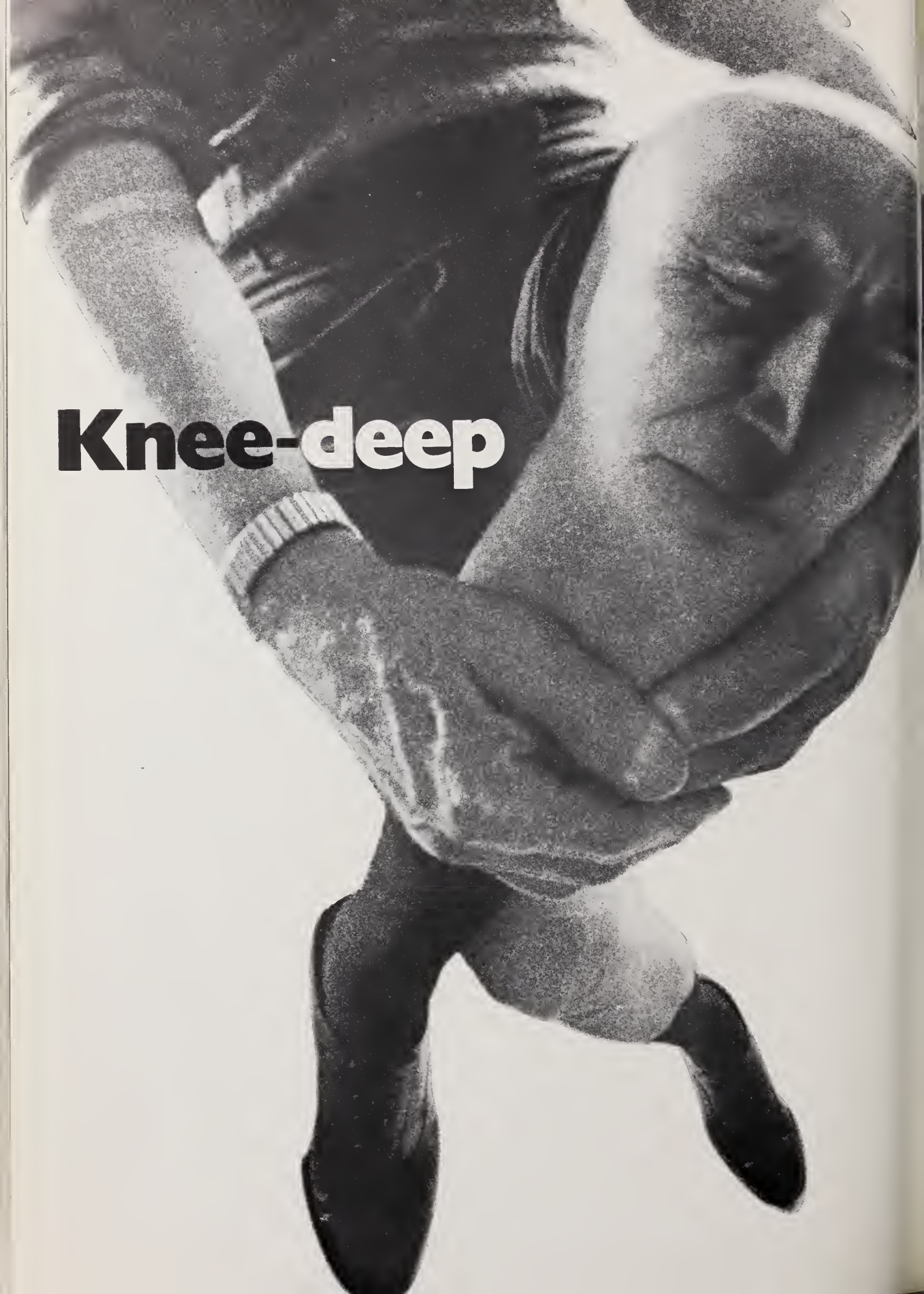
ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.


Knee-deep

in osteoarthritic pain

If aspirin doesn't help, move in with Tandearil.

The trial period is brief: 1 week. Try one tablet q.i.d. at first. Tandearil usually starts working within 3 to 4 days. When response occurs, as little as 1 or 2 tablets daily may hold back pain and stiffness, and increase joint motion.

On the next page is a summary of adverse reactions, contraindications, warning and precautions.

Tandearil.
It can help get his mind off his knee.

Please review full Prescribing Information carefully before prescribing.

For osteoarthritic knees, spines, shoulders, hips, etc.:

Tandearil®
oxyphenbutazone

andearil, oxyphenbutazone:
or brief summary see next page.

Geigy



Tandearil®
oxyphenbutazone

Contraindications: Edema; danger of cardiac decompensation; history or symptoms of peptic ulcer; renal, hepatic or cardiac damage; history of drug allergy; history of blood dyscrasia. The drug should not be given when the patient is senile or when other potent drugs are given concurrently.

Warning: This drug is an analog of phenylbutazone; sensitive patients may be cross-reactive. If coumarin-type anticoagulants are given simultaneously, watch for excessive increase in prothrombin time. Instances of severe bleeding have occurred. Persistent or severe dyspepsia may indicate peptic ulcer; perform upper gastrointestinal x-ray diagnostic tests if drug is continued. Pyrazole compounds may potentiate the pharmacologic action of sulfonylurea, sulfonamide-type agents and insulin. Carefully observe patients receiving such therapy. Use with caution in the first trimester of pregnancy, and in patients with thyroid disease.

Precautions: Before prescribing, carefully select patients, avoiding those responsive to routine measures as well as contraindicated patients. Obtain a detailed history and a complete physical and laboratory examination, including a blood count. The patients should not exceed recommended dosage, should be closely supervised and should be warned to discontinue the drug and report immediately if fever, sore throat, or mouth lesions (symptoms of blood dyscrasia), sudden weight gain (water retention), skin reactions, black or tarry stools or other evidence of intestinal hemorrhage occur. Make complete blood counts at weekly intervals during early therapy and at 2-week intervals thereafter. Discontinue the drug immediately and institute countermeasures if the white count changes significantly, granulocytes decrease, or immature forms appear. Use greater care in the elderly and in hypertensives.

Adverse Reactions: The more common are nausea and edema. Swelling of the ankles or face may be minimized by withholding dietary salt, reduction in dosage or use of diuretics. In elderly patients and in those with hypertension, the drug should be discontinued with the appearance of edema. The drug has been associated with peptic ulcer and may reactivate a latent peptic ulcer. The patient should be instructed to take doses immediately after meals or with milk to minimize gastric upset. Drug rash occasionally occurs. If it does, promptly discontinue the drug. Agranulocytosis, exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), or a generalized allergic reaction similar to a serum sickness syndrome may occur and require permanent withdrawal of medication. Agranulocytosis can occur suddenly in spite of regular, repeated normal white counts. Stomatitis, salivary gland enlargement, vomiting, vertigo and languor may occur. Leukemia and leukemoid reactions have been reported. While not definitely attributable to the drug, a causal relationship cannot be excluded. Thrombocytopenic purpura and aplastic anemia may occur. Confusional states, agitation, headache, blurred vision, optic neuritis and transient hearing loss have been reported, as have hyperglycemia, hepatitis, jaundice, hypersensitivity angiitis, pericarditis and several cases of anuria and hematuria. With long-term use, reversible thyroid hyperplasia may occur infrequently. Moderate lowering of the red cell count due to hemodilution may occur.

Dosage in Osteoarthritis: Initial: 3 to 6 tablets daily in divided doses. Usually unnecessary to exceed 4 tablets daily. A trial period of one week is considered adequate to determine the therapeutic effect of the drug. Maintenance: Effective level often achieved with 1 or 2 tablets daily, should not exceed 4 tablets daily.

In selecting appropriate dosage in any specific case, consideration should be given to the patient's weight, general health, age and any other factors influencing drug response.

Availability: Tan, round, sugar-coated tablets of 100 mg. in bottles of 100 and 1000.

(B)R-46-800-A

For complete details, please see full Prescribing Information.

Geigy Pharmaceuticals
Division of
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Ardsley, New York 10502

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ASOCIACION MEDICA DE PUERTO RICO

ORGANO OFICIAL

Fundado en 1903

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Anuncios y Suscripciones:
El Boletín se publica mensualmente. El precio de suscripciones es de $5.00 por año. Todo material de anuncio está sujeto a aprobación por la Junta Editora.

Reimpresos:
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TRANSVENOUS INTRACARDIAC PACING WITH EXTERNAL PACEMAKER

A. Sánchez Valentín, MD
P. Crenshaw-Rivera, MD

During the last years the use of electrical pacing of the heart has been of enormous value in the management of several conditions associated with a decreased effective cardiac output. Several of these conditions are extremely serious and carry a high mortality and morbidity. The clinical picture of these conditions may range from episodes of dizziness, fainting, light headedness, convulsions, marked dyspnea on exertion, behavior disturbances, to sudden death.

Although it had been a known fact that electrical stimulation of the heart could elicit myocardial contraction, this information was not successfully applied to human beings until 1952 when Zoll and associates reported pacing of the heart in a patient, using external transthoracic electrical stimulation (1).

In 1957 Weirich, Gott, and Lillehei used myocardial pacemakers to control the heart rate in patients with surgically induced heart block (2). A year later Furman and Robinson reported on the use of a transvenously introduced unipolar catheter to control the heart rate; (3) Chardack *et al* in 1960 introduced the use of a subcutaneously implanted powered circuit connected to electrodes implanted in the epicardial surface of the heart (4).

During the last few years a variety of devices have become commercially available for cardiac pacing using internal or external control circuits. We may classify pacemakers into two major groups; internal and external. External pacing is accomplished by applying electrodes directly to the chest wall and discharging an electric current to the heart across the intact chest wall. This method is very uncomfortable and painful and is reserved for short periods of time until internal pacing can be instituted.

Internal cardiac pacing may be instituted by three main methods: 1) via electrodes implanted directly to the epicardium, 2) through unipolar or bipolar electrodes which are introduced via the venous system into the right ventricular cavity, thus stimulating the endocardial surface, and 3) by the percutaneous insertion of electrode wires through the chest wall. The source of power for these electrodes may be located externally or may be implanted beneath the skin.

At the present time external pulse generators are preferred for temporary pacing with the exception of a radiofrequency type of apparatus where impulses are transmitted from an externally located pulse generator into an implanted receiver whose electrodes will stimulate the heart either epicardially or endocardially (5).

Depending on the time when the pacemaker

From the Cardiopulmonary Laboratory, University Hospital and the Coronary Care Unit, Presbyterian Community Hospital, San Juan, Puerto Rico.

Read during Annual Convention of the Puerto Rico Medical Association in November 1967.

impulse is delivered to the myocardium pacemakers can also be classified into synchronous and asynchronous (6). In the system of synchronous pacing, the pacemaker is activated by the atrial depolarization. The atrial impulse will be amplified and thus will be transmitted to the ventricles acting as an extracardial bundle of His. This method is indicated in patients with complete heart block and regular atrial activity. It is more physiological since the atrial contraction immediately preceding the electrically induced ventricular contraction will increase the cardiac output (7). It is not used very extensively at the present because its system is more complicated and thus, more liable to technical failure.

In asynchronous pacing the time of the electrical ventricular stimulation will be independent from the time of atrial contraction.

There are three types of asynchronous pacemakers available, 1) fixed rate, 2) variable rate and, 3) "demand or standby".

Fixed rate pacemakers consist of a pulse generator which fires an electric current at a rate which is set by the manufacturer. These were more frequently used during the early years and gave way to the variable rate and current control pacemakers in which the rate and strength of the stimulating current may be controlled according to the physiologic needs of the patient (8).

More recently a "demand" or "standby" pacemaker is becoming very popular in patients with heart block who may show competition between spontaneous beats and pacemaker induced beats (9). This is very important since evidence is mounting that a number of "unexplained" deaths occurring after implantation of pacemakers may have been due to arrhythmias occurring when the pacemaker stimulation occurs on the vulnerable period of the ventricle. Demand pacemakers contain a basic pulse generator and a "sensing-cancelling" mechanism which is selectively tuned to the characteristic slope of the QRS complex and distinguishes it from either P or T waves. The demand pacemaker will remain dormant as long as the spontaneous heart rate exceeds the preset rate of the unit. Whenever the interval following a QRS complex exceeds the "repolarization" time of the artificial pacer it will automatically start sending electrical impulses to the myocardium. It will continue working as a fixed rate cardiac pacemaker unless spontaneous ventricular activity at a faster rate (than the pacemaker) appears.

We will discuss our experience at the University District Hospital on the emergency use of transvenous endocardial pacing with catheter electrodes connected to an external pulse generator.

Material and Methods

In the time interval between September 6, 1965 and August 31, 1967 electrical pacing of the heart was attempted in 13 patients as an emergency measure. The procedure was done by the members of the cardiovascular team at the Cardiopulmonary Laboratory. Under local Xylocaine anesthesia a bipolar Goetz number 6 electrode was introduced into the right median antecubital vein. With the aid of an image amplifier and continuous cardiac monitoring the catheter was advanced into the right chambers of the heart as far as the main pulmonary artery (this as a precaution to avoid placing the catheter in the coronary sinus). The catheter was then withdrawn and left imbeded in the trabeculae at the apex of the right ventricle. The catheter was connected to an external Medtronic number 5870 pulse generator with variable rate and current control. The pacemaker rate was usually kept between 65 to 75 impulses per minute and the voltage used was the lowest which would elicit an adequate regular ventricular response.

A great majority of these patients were critically ill and the procedure was done as a heroic measure. Usually there was a need for a rapid performance of the procedure under sub optimal conditions. Endovenous pacing usually was continued until the patient had a permanent pacemaker implanted or when the indications for pacing disappeared.

Report of Cases

Case 1:

An 86-year old female was admitted on September 6, 1965 because of multiple (20-25) episodes of Stokes-Adams seizures during the last 8 hours. Six years previously she had developed symptoms of congestive heart failure and during the last three years she had history of dizzy spells and occasional convulsive seizures. She had received treatment previously with isoproterenol, ephedrine, and atropine, digitalis and pentaerythritol Tetranitrate (Peritrate).

Physical examination on admission revealed a conscious, cooperative elderly female with frequent episodes of unconsciousness. Blood pressure was 180/40 and the heart rate was 44/minute. The heart sounds were heard distantly and the first heart sound was found to have a variable intensity. Electrocardiogram showed complete heart block with occasional runs of ventricular tachycardia.

Treatment with atropine was to no avail, so on the same day an endovenous bipolar electrode pacemaker was inserted. During the procedure she had 5 episodes of Stokes–Adams seizures due to ventricular fibrillation which responded to external cardiac massage and electrical defibrillation. At a pacing rate of 80/min. frequent ectopic ventricular contractions were observed but they could be almost completely abolished at a pacing rate of 90/minute. Two days after insertion of the pacemaker, ectopic contractions appeared, and they were suppressed with procaine amide.

A permanent endovenous pacemaker was implanted on 9/9/65 and the patient was discharged on September 13th on digitalis maintenance. She was doing well when seen for the last time in follow up.

This case shows how dramatic the effect of electrical cardiac pacing can be. This patient had many factors of grave prognosis, and was in critical condition. Nevertheless she is doing well 2 years after having the permanent pacemaker implanted.

Case 2:

A 41-year old diabetic dependent, wife of a naval officer was doing well until two weeks prior to admission when she developed symptoms of an upper respiratory infection. Few days later she was examined by a physician who noticed an irregular pulse of 72/min. By the next day she had symptoms of congestive heart failure. EKG revealed complete heart block with multifocal ectopic rhythm (See Fig. 1).

On the following day August 3, 1966, she became cold, clammy, her heart rate dropped to 20/min. and her blood pressure became unobtainable. Isoproterenol infusion increased her pulse to 50/min. and her blood pressure to 80/60.

She had a short period of asystole in the emergency room. EKG revealed complete A-V block with multifocal ventricular contractions and occasional runs of ventricular tachycardia.

An endovenous pacemaker was inserted immediately on arrival and adequate pacing was established. She continued treatment with prednisone, digoxin, and insulin. Two days after admission the EKG showed sinus rhythm with 1st. degree A-V block and the pacemaker was removed. At the time of discharge the EKG showed 1st. degree A-V block and right bundle branch block.

This case demonstrates how a pacemaker can be of utmost help in cases with transient yet life threatening heart block.

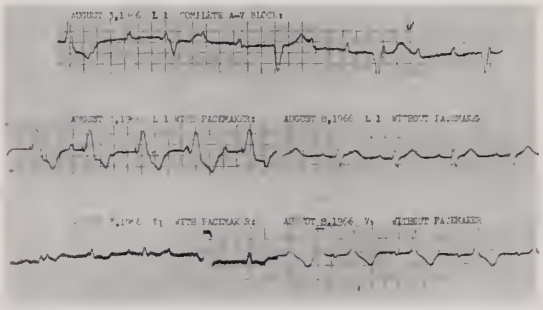


Fig. 1: Top tracing shows A-V block with slow ventricular rate. The lower 2 tracings show leads I and V_1 during cardiac pacing and after removal of pacemaker (shows prolonged P-R interval and right bundle branch block).

Case 3:

A 14-year old male was admitted on October 31, 1966 after an episode of unconsciousness associated with cold sweat, difficulty in breathing and cyanosis.

He had suffered from similar episodes since the age of 4 months. At the age of 4 yrs. the diagnosis of complete heart block was done, and during the last year he had been on ephedrine and isoproterenol which had decreased the frequency of the

attacks.

Physical examination on admission revealed a well nourished, well developed young man in no distress. The blood pressure was 178/84 mm Hg and the pulse was 44/min. Examination of the heart revealed a left ventricular thrust, cardiomegaly and a grade III harsh systolic murmur in the left sternal border and at the apex.

On November 1, 1966 an endovenous pacemaker was implanted into the right ventricular outflow tract and efficient pacing was obtained. On November 4th permanent epicardial pacemaker was implanted.

The patient was asymptomatic when seen in clinic for the last time on August 25, 1967. He is pending studies to rule out the diagnosis of congenital heart disease. In this patient the pacemaker was introduced to control the heart rate during the procedure of insertion of the epicardial pacemaker which required a thoracotomy.

Case 4:

An 82-year old male was referred on December 8, 1966 to the UDH Surgical Department after having Stokes-Adams seizures following facial surgery to remove a squamous cell carcinoma.

EKG on admission revcaled complete A-V block with a ventricular rate of 54/min. He was treated with Isoproterenol infusion with no improvement. While in the surgical ward he had multiple episodes of Stokes-Adams seizures due to runs of ventricular tachycardia and ventricular fibrillation requiring electrical defibrillation on more than 20 occasions.

On December 22, 1966 he had an intravenous number 6 Goetz bipolar catheter implanted in the right ventricle. During the procedure he had repeated episodes of convulsions due to ventricular tachyarrhythmias, requiring more than 15 electrical shocks. Adequate pacing was obtained at a rate of 75/minute.

About 2 hours later intermittent pacing was noted allowing the occurrence of ventricular tachycardia, and fibrillation. This required again electrical defibrillation. He was brought back to the cardiopulmonary laboratory where fluoroscopic examination revealed the catheter to be at the level of the tricuspid valve. Adequate pacing was obtained when the tip of the catheter was placed again in the right ventricular trabeculae. On December 13th he had one run of ventricular tachycardia with convulsions, and on the following day he developed difficulty in breathing and went into cardiac arrest. He did not respond to resuscitative measures.

Case 5:

A 42-year old TV actress was admitted on January 31, 1966 because of history of unconsciousness and dizzy spells. She had history of severe rheumathoid arthritis for 12 years. Five years ago she was told to have a heart murmur and right bundle branch block.

During the last four years her arthritic symptoms had been controlled with chloroquine. In October 1966 she had an episode of unconsciousness and 2 months later she developed short episodes of dizzy spells and unconsciousness. EKG revealed normal sinus rhythm. In January 1967 during one of the episodes of unconsciousness EKG showed complete heart block. She had no response to treatment with propantheline bromide (Probanthine), isoproterenol and steroids and in January 31, 1967 she was transferred to the UDH.

On physical examination she was found to have a blood pressure of 120/80 mm Hg and a pulse of 40/min. A grade I systolic murmur was heard along the left parasternal region. Typical changes of severe rheumatoid arthritis were noted in both wrists and hands. An endovenous pacemaker was inserted and adequate pacing was obtained. During the first days she had complete heart block alternating with episodes of normal sinus rhythm. After the fourth day she remained in complete heart block requiring constant pacing. Medications were then discontinued.

On December 17, 1967 a permanent endovenous Medtronic pacemaker was implanted, and she was soon discharged in good condition. Since then she has had multiple symptoms due to her underlying disease but pacing has been adequate throughout.

Case 6:

This 49-year old male was admitted on February 5, 1967 because of disorientation of five days duration. During the previous 2-3 days he had complained of occasional chest pain, dyspnea on exertion, dizzy spells without loss of consciousness.

Physical examination revealed a well developed, well nourished male looking older than his stated age. He was uncooperative, very disoriented and aphasic. The blood pressure was 100/60 mm Hg and the pulse was 40/min. Examination of the heart revealed cardiomegaly and a short systolic murmur in the left parasternal region.

He was treated with steroids to no avail but Isoproterenol infusion could increase his pulse to 60-80/

minute.

On February 12th a temporary endovenous catheter was implanted in the apex of the right ventricle at a rate of 80/min. That night he had a right femoral embolus and embolectomy was performed. On February 27th another endovenous pacemaker was introduced (See Fig. 2).

Mentation started improving very slowly after five weeks of endovenous pacing. On March 16th a permanent endovenous pacemaker was implanted and the patient was discharged much improved. Few weeks later cellulitis was noted in the right pectoral region over the power pack. This progressed to sloughing of the skin. Eventually the power pack was removed, resterilized and reimplanted on the other side of the chest.

At the present the patient is doing well.

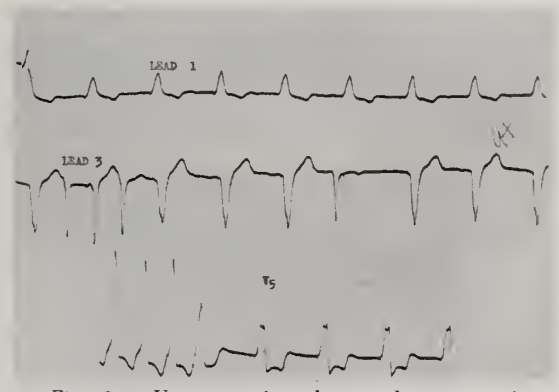


Fig. 2: Upper tracing shows adequate pacing. Lower tracings show frequent premature ventricular contractions which at times interfere with the artificial stimulation of the heart. A run of ventricular tachycardia is seen in V5.

Case 7:

This 79-year old female was referred because of severe respiratory distress. She had been having symptoms of cardiac decompensation since 1952 and had been treated with digoxin, KCL, and diuretics. She had history of myocardial infarction in 1952, 1960, and 1966.

One week prior to admission she developed cough with expectoration, and marked shortness of breath. She was hospitalized at the local Health Center where she was treated with penicillin and streptomycin. Since her condition continued downhill she was referred for admission to the University Hospital. On arrival to the emergency room she was found to have complete heart block with a pulse of 40/minute.

While receiving an isoproterenol infusion she developed a supraventricular tachycardia. Lanatoside-C was administered and the tachycardia reverted to first degree A-V block, second degree A-V block and then to ventricular standstill.

Subsequently she developed cardiac arrest responding to external cardiac massage and Isuprel infusion.

Physical examination revealed a thin, small female who was excited, restless, and incoherent. On arrival to the ward the blood pressure was 150/68 and the heart rate was 114/min. The rest of the physical examination was essentially negative.

During the first 24 hours she had 11 episodes of cardiac standstill which responded to external cardiac massage and isoproterenol infusion. EKG revealed complete A-V block changing to supraventricular tachycardia, to A-V dissociation with frequent multifocal ventricular contractions and back to complete A-V block.

On the next day a temporary endovenous pacemaker was inserted into the right ventricle and adequate pacing was obtained. Nevertheless she became oliguric and had no response to mannitol infusion. On January 18, 1967 she was found apneic and no ventricular response could be elicited by the pacemaker stimulus in spite of increasing the voltage to the maximum of the power pack.

Autopsy revealed pulmonary edema, bronchopneumonia, congested liver and kidneys. There was evidence of old anterior and posterior myocardial infarctions.

The coronary arteries were patent but the lumen was diminished in size in 60-70 percent in some segments and markedly affected by arteriosclerosis.

Case 8:

A 65-year old patient was admitted because of dizziness, nausea and vomiting of one day duration.

For two years she had been known to be hypertensive and had signs and symptoms of congestive heart failure. Two days prior to admission she had an episode of dizziness and epigastric pain radiating to the left subcostal area, associated with nausea, vomiting and diaphoresis which lasted for two hours.

Physical examination revealed a well developed, thin mulatto female in moderate distress. She had

a blood pressure of 180/104 mm Hg and a pulse of 56/min. She had cardiomegaly and a grade I short apical systolic murmur. EKG revealed complete A-V block with negative T waves in the whole precordium and occasional premature ventricular contractions (See Fig. 3).

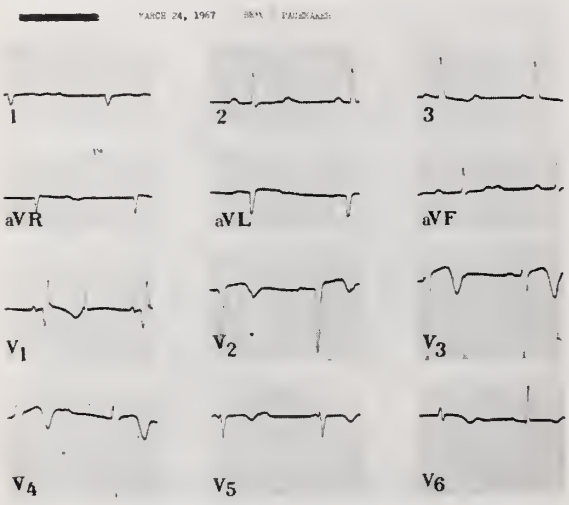


Fig. 3: There is complete A-V block, giant negative T waves and probably an occasional conducted beat (see V_6 and L2).

Isoproterenol infusion suppressed the ventricular extrasystoles and increased the rate. On March 25, 1967 a temporary intravenous pacemaker was introduced into the right ventricle pacing at a rate of 75/min. Several days later local infection was noted at the point of entrance of the catheter. Infection was controlled promptly with antibiotics (See Figs. 4 and 5).

On April 24, 1967 a permanent endovenous pacemaker was implanted and the patient was discharged five days later in good condition. A few weeks after discharge she was found to have irregular pulse, and admission for reevaluation was ordered. While being examined on arrival to the ward she had an episode of Stokes-Adams. EKG revealed artificial pacing at a rate of 75/min. interrupted by aberrant complexes probably representing conducted beats from an atrial tachycardia of 280-300/min. Subsequently, she developed episodes of 2:1 A-V block, and complete A-V block with idioventricular rhythm.

On examination the catheter tip was found to be at the tricuspid valve area and a partial break was seen in one of the electrodes wires. Adequate

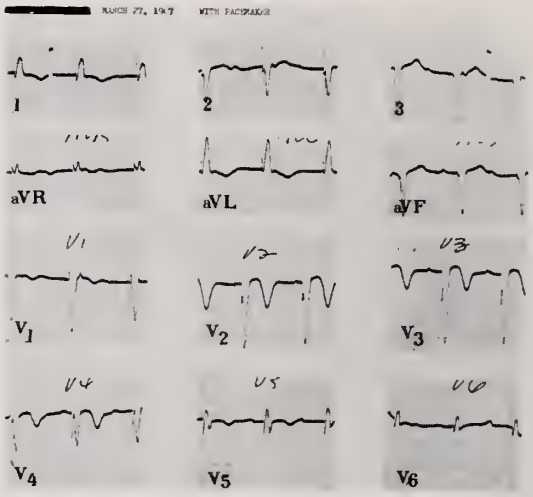


Fig. 4: Following pacemaker well. Note that the configuration of the QRS complexes is different from Fig. 3. This is due to the fact that depolarization of the heart starts at the right ventricular apex- the site of electrical stimulation.

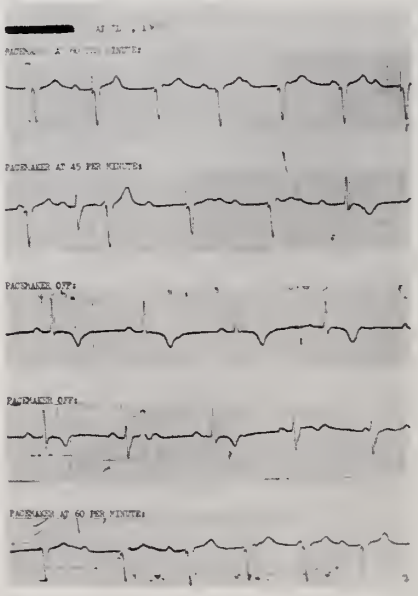


Fig. 5: Note that in the first and last tracing she "follows" the pacemaker stimulus well. At lower rates, spontaneous ventricular activity will be manifested; this can be overcome by increasing the rate of electrical stimulation to 60/min.

pacing was established by repositioning the catheter tip in the right ventricular apex and fixation of the catheter to prevent further kinking of the damaged area. Patient was doing well when last seen in clinic on 6/9/67 (See Fig. 6).

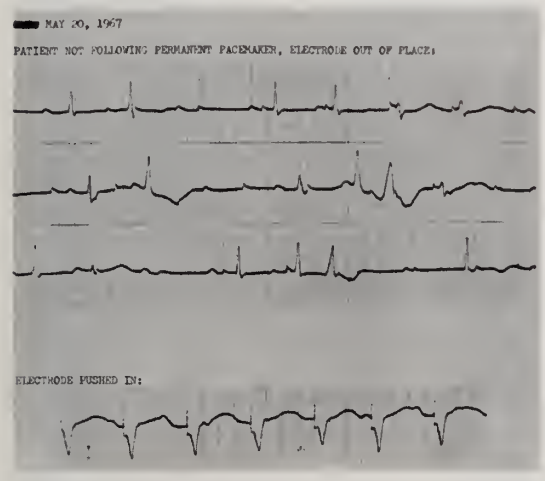


Fig. 6: Upper tracings show inadequate pacing due to spontaneous migration of electrode to the tricuspid valve area. Repositioning of tip into the right ventricle re-established adequate pacing.

Case 9:

A 90-year old male was admitted to the University Hospital on May 3, 1967 because of giddiness of 5 days duration, chest pain and respiratory distress.

Physical examination revealed a blood pressure of 170/90 mm Hg and a pulse of 50/min. He was conscious, cooperative but on occasions he spoke incoherently and became disoriented. EKG revealed complete heart block. Occasional moist rales were heard on auscultation.

Solu-Cortef®, intravenous isoproterenol, and digoxin were given to no avail. On May 6, 1967 a temporary endovenous pacemaker was implanted in the apex of the right ventricle. Adequate myocardial response to the pacemaker was obtained, and at a rate of 75/min. Subsequently erratic pacing reappeared and it could not be controlled in spite of increasing the milliamperage to its maximum of 6 ma. He also developed swelling and redness in the arm where the catheter electrode had been introduced. The catheter electrode was removed on May 8, 1967 because of persistence of erratic pacing. The patient died 5 days later after an episode of respiratory distress. No autopsy permission could be obtained from the relatives.

Case 10:

This 82-year old female was admitted to the UDH on March 14, 1967 with history of confusion of 6 days duration following an episode of unconsciousness, convulsions, and cyanosis. In 1961 she was admitted to the University Hospital where she was found to have a 2:1 A-V block. Normal sinus rhythm reappeared in a few days, but in 1962 she developed complete A-V block.

She was treated with isoproterenol 10 mg tid. During the next 3 years she had occasional episodes of unconsciousness and dizzy spells. She refused pacemaker implantation on several occasions.

Six days prior to admission she developed an episode of Stokes-Adams. She was examined at the local health center where she was found to have a blood pressure of 220/110 mm Hg. On March 14, 1967 she was referred to us after an episode during which she became arreflexic; and no vital signs could be recorded. External cardiac massage was successfully applied (See Fig. 7).

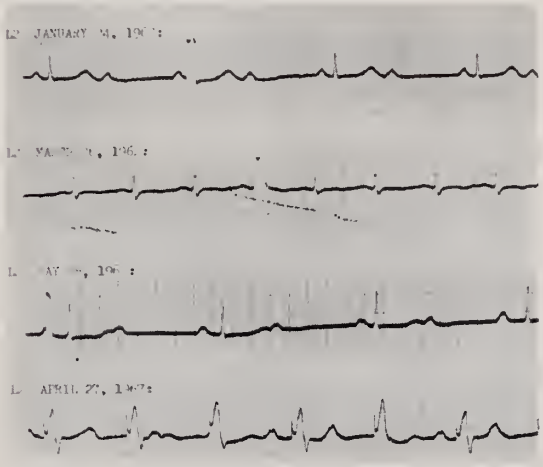


Fig. 7: These tracings show the clinical course of this patient during 5 years. First tracing shows 2:1 A-V block. Second tracing shows 1:1 conduction while isoproterenol was being administered. Third tracing shows complete A-V block. Fourth tracing shows adequate electrical pacing.

Physical examination on arrival revealed a blood pressure of 180/60 and a pulse of 40/min. EKG revealed complete A-V block with giant negative T waves in V5. She did not respond to Isoproterenol infusion. Next day a temporary endovenous catheter pacemaker was implanted into the right ventricular apex. Adequate pacing was obtained at a rate of 70/min., but nevertheless no marked improvement was noted in her mental condition until 5 days later. She developed irregular pacing and X-rays showed that the catheter tip had been displaced into the right ventricular outflow tract. Adequate pacing was obtained after withdrawal of the catheter and imbeding its tip in the trabeculae of the right ventricle (See Figs. 8, 9 and 10).

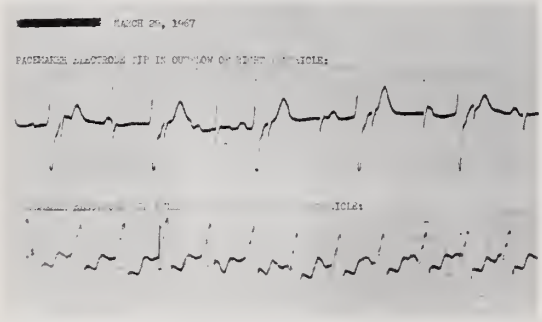


Fig. 8: Top tracing shows inadequate pacing when the electrode tip migrated into the outflow of the right ventricle. In lower tracing a good response was obtained upon withdrawal of the catheter into the right ventricle.

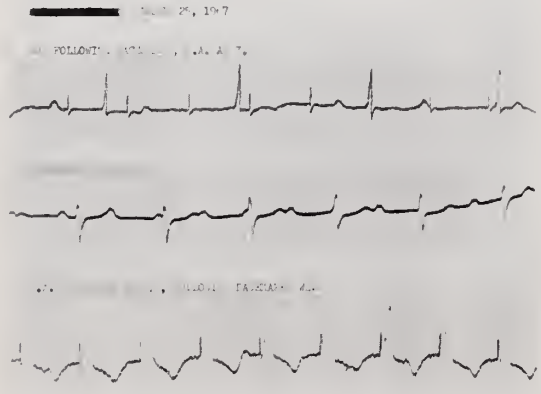


Fig. 9: The top tracing shows inadequate pacing with a stimulus of 3 milliamperes. In the lower tracing adequate pacing is obtained by increasing the stimulus to 6 milliamperes.

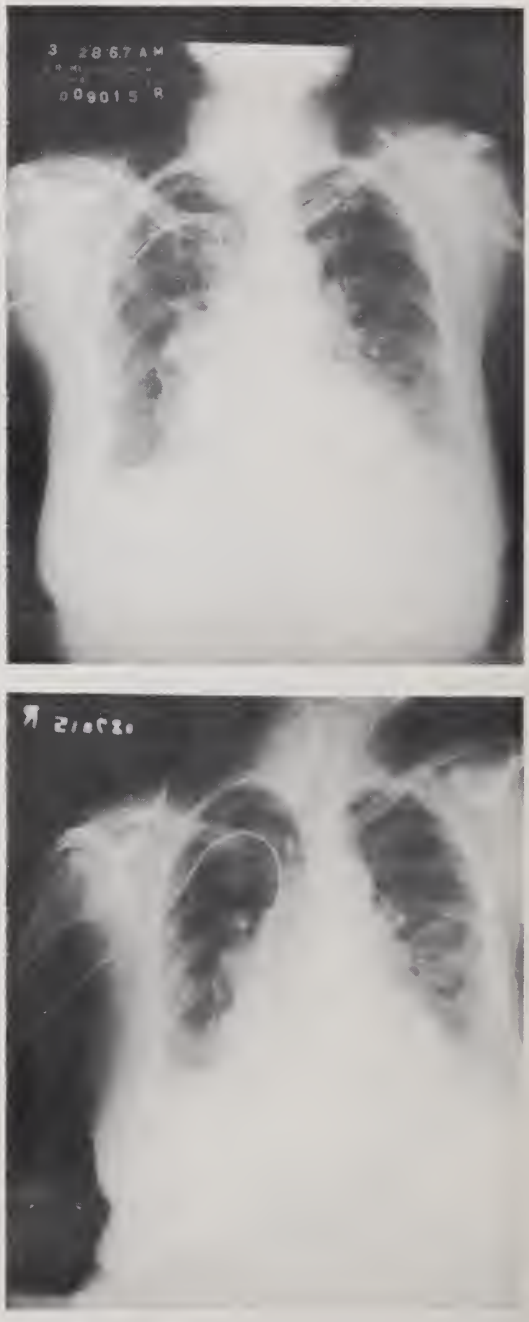


Fig. 10: A- Catheter tip is noted in the right ventricular outflow (inadequate pacing). B- Catheter tip after being pulled into the right ventricle (adequate pacing).

Weeks later a permanent endovenous pacemaker was implanted and pacing was obtained at a rate of 67/min. She was discharged in good condition.

One month later she was readmitted in stuporous condition with history of bloody diarrhea of 2 days duration which had been preceded by abdominal pain of one week duration. She went into hypotension, coma and became anuric. The pacemaker was being followed well. On the next day she developed short runs of ventricular tachycardia which subsided spontaneously. Serial EKG's showed progressive widening of the QRS and decreasing voltage of the QRS. Next day she died and post mortem examination revealed an acute myocardial infarction and severe coronary atherosclerosis. There was also evidence of an acute focal necrotizing enterocolitis. The pacemaker electrode was in good position in the right ventricle.

Case 11:

A 75-year old female was admitted on June 2, 1967 because of abdominal discomfort and diaphoresis of seven hours duration. Three hours after the onset of these symptoms she noticed weakness and dizziness.

On arrival she had a pulse of 45/min. and the blood pressure ranged from 180/100 to 80/0 mm Hg. She was incoherent and confused. The skin was cold and sweaty. EKG revealed complete A-V block. She received Cedilanid, and Isoproterenol which increased the pulse to 52-96/min.

An intravenous catheter electrode was introduced on the same day, and adequate pacing was obtained at a rate of 75/min. She became conscious and oriented. In spite of treatment with vasopressors the blood pressure remained low, and her urine output was markedly diminished.

Four hours after the insertion of the pacemaker she complained of chest pain, became incoherent and the blood pressure became unobtainable and died. The pacemaker was noted to continue working but no myocardial activity could be recorded. Post mortem examination revealed acute and old posterior myocardial infarctions, left ventricular hypertrophy and severe coronary arteriosclerosis.

Case 12:

This 85-year old female had history of an acute myocardial infarction in 1959. She had history of having been admitted in congestive heart failure in one occasion. The patient had been under treatment with digitalis and antihypertensives until 2 days prior to admission.

On the night of June 22, 1967 she developed dyspnea, cyanosis, and precordial pain radiating to the left arm. On arrival to the emergency room she had a blood pressure of 110/70, an apical rate of 142 and an irregular radial pulse of 92/minute.

The neck veins were engorged and examination of the heart revealed left ventricular accessibility. Moist rales were heard in both lungs. She received treatment with morphine sulfate, salyrgan, and oxygen.

EKG revealed inferolateral ischemia and runs of atrial fibrillation with fast ventricular response and frequent premature ventricular contractions and episodes of asystole. Pronestyl was unsuccessfully used in an effort to control the tachyarrhythmia. Electrical cardioversion was attempted in several occasions and she would develop a chaotic rhythm.

Endovenous cardiac pacing was attempted but adequate pacing could not be established because of mechanical difficulties. The patient died a few hours later in cardiac arrest.

Post mortem examination revealed pulmonary edema, moderate coronary arteriosclerosis without stenosis or obstruction, moderate cardiac dilatation. No evidence of old or recent myocardial infarction was seen.

Case 13:

This 50-year old patient (brother of patient number 6) was admitted on July 22, 1967 because of symptoms of congestive heart failure and mild chest pain on exertion. Six days before admission he had an episode of severe substernal chest pain associated with dyspnea. The pain subsided spontaneously and reappeared three days later. No history of dizzy spells, of convulsions.

Physical examination on admission revealed a well developed, well nourished male who was diaphoretic

and cold. He was conscious and cooperative. The pulse was 60/min and the blood pressure was 100/70 mm Hg. He was in heart failure and had cardiomegaly. EKG revealed complete A-V block.

The severity of the congestive heart failure was not altered with the treatment with digitalis and the central venous pressure ranged between 30.5 and 36.5 cms. of water.

One day after admission an endovenous catheter electrode was inserted into the apex of the right ventricle. Adequate pacing was established at a rate of 80/min., nevertheless the heart failure failed to improve.

Four days later shock developed and he became lethargic. Treatment with aramine increased his blood pressure and he became alert.

Some hours later the blood pressure became unobtainable and no response could be obtained with the use of aramine and Isuprel. The patient died some minutes later. At the moment of death the pacemaker artifact could be demonstrated in the oscilloscope but no ventricular response could be noted. Post mortem showed a posterior myocardial infarction.

Results

Patient population:

In our series the ages ranged from 14-96 years. Eight out of 13 were between 65-95 years. The duration of paeing varied from few hours to 34 days.

Indications for pacing:

The indications were (see Table I): Seizures in 7, mental confusion or dizziness in 5, and intractable heart failure in one patient.

Complete heart block was present in 12 of the 13 patients. Patient number 12 had atrial fibrillation with a very fast ventricular response, frequent premature ventricular contractions alternating with ventricular tachycardia and cardiac arrest.

Complete heart block was in many instances associated with episodes of normal sinus rhythm, ventricular tachycardia, premature ventricular contractions, varying degrees of A-V block and cardiac arrest.

Probable etiology of the heart disease:

The following conditions, the presence of which has been associated with the occurrence of heart block were seen in our patients (table II); severe coronary artery disease by autopsy, by history, or by EKG findings, upper respiratory infection associated with myocarditis, congenital heart disease, and rheumatoid arthritis.

TABLE I: INDICATIONS FOR PACING

Indication	Number
Stokes - Adams seizures	7
Mental confusion	2
Mental confusion and dizziness	3
Intractable heart failure	1

TABLE II: ETIOLOGY

Probable Etiology	Number
Coronary artery disease	4
Coronary artery disease; familial conduction defect ?	2
Rheumatoid arthritis	1
Myocarditis	1
Congenital heart disease	1
Undetermined	4

Complications:

In three out of 13 patients adequate sustained pacing could not be established. In one patient the pacing was interrupted by frequent premature ventricular contractions, and in another patient the response to pacing was erratic. In some patients the ectopic contractions could be suppressed by increasing the rate of the pacemaker pulse generator. Localized mild

infection at the point of entrance of the catheter occurred in two patients. It was easily controlled with antibiotics.

Erratic pacing was observed in two patients because of migration of the catheter, into the right atrium and into the right ventricular outflow tract. Sustained pacing could be obtained after correction of the catheter position.

Mortality:

Four of our patients died during the phase of temporary pacing (numbers 4, 7, 11, 13). In the first three patients the clinical course had been affected by severe complications such as repeated ventricular tachycardia, ventricular fibrillation, arrests, and block.

In the fourth patient an acute inferior myocardial infarction was found in the post mortem examination.

Two patients died a few days after the removal of the catheter, adequate pacing could never be obtained in them. Patient number 10 died 1 month after the insertion of a permanent endovenous pacemaker.

Discussion

For the last few years, the timely institution of electrical cardiac pacing has been a determinant factor in decreasing the mortality and morbidity in several conditions characterized by a transitory or a chronic decrease in effective cardiac output. As pacemakers are constantly being improved technically and the indications for their use more clearly defined, better results are being obtained.

The most frequent indication for electrical pacing of the heart is complete heart block associated to seizures, intractable heart failure, changes in personality, or dizzy spells. They have also been beneficial in: symptomatic sinus bradycardia; sinus arrest; atrial flutter, fibrillation or tachycardia; for the prevention of ventricular ectopic contractions, ventricular tachycardia, or fibrillation.

The occurrence of heart block has been associated to several conditions such as: sarcoidosis, lues, tuberculosis, diphtheria, rheumatoid arthritis, hypertension, infiltration of the conduction system by fat or by calcium deposits, amyloidosis, rheumatic heart disease, coronary artery disease (especially after inferior myocardial infarction). Recent anatomo pathological studies revealed a high percentage of heart block associated with diffuse fibrosis in the myocardium. Families in which several members suffer from disturbances of conduction have been reported.

In spite of the ease with which endovenous pacing may be accomplished, the procedure is not free of complications. Some of these are: perforation of the myocardium, pulmonary air embolism, erratic pacing due to migration of the catheter electrode, phrenic nerve stimulation (may produce hiccups), epileptic seizures, tachyarrhythmias, localized or generalized infections. Fatal ventricular arrhythmias have been known to occur when the pacemaker impulses are discharged during the ventricular "vulnerable period". Several of these complications were seen in our patients.

Seven of our patients have died, four of them during the first days of endovenous pacing. Two other patients died after the pacemakers were removed because adequate pacing could never be obtained. The seventh patient died one month after insertion of a permanent pacemaker (was found to have an acute myocardial infarction and a necrotizing enterocolitis).

In our experience the emergency use of temporary endovenous pacing has been extremely rewarding since we have been able to prolong useful life in six patients who would have previously been considered far beyond the reach of medical therapy.

The fact that 46 percent of these patients

are still alive is both satisfying and encouraging.

Summary

We have reported our experience with 13 patients in which emergency temporary endovenous cardiac pacing was attempted at the University Hospital. The endovenous cathcter-electrode was inserted through the right median antecubital vein and advanced with the aid of an image amplifier until embedded in the trabeculae of the right ventricle.

In two of these patients adequate pacing could never be obtained, and eventually they died.

Four other patients died during the first days in spite of adequate pacing. The seventh patient died one month after having a permanent pacemaker implanted. Autopsy revealed an acute myocardial infarction and necrotizing enterocolitis. The pacemaker was functioning well at the time of her death.

Six of these patients are still alive.

We feel that the results obtained with temporary endovenous cardiac pacing are very rewarding and encouraging since we were able to control the symptoms caused by heart block until a permanent pacemaker could be implanted or until the block had disappeared.

Resumen

Se reporta nuestra experiencia en el uso temporero de marcapasos eléctricos endovenosos en 13 pacientes críticamente enfermos. El electrodo es introducido a través de la vena mediana antecubital derecha y con la ayuda de un amplificador de imágenes es avanzado hasta dejarse en el ápice del ventrículo derecho.

No fue posible obtener respuesta ventricular adecuada en dos pacientes y estos murieron. Otros cuatro pacientes murieron durante los primeros días a pesar de haberse obtenido una respuesta ventricular adecuada al estímulo del marcapasos.

Una séptima paciente murió un mes después de habérsele implantado un marcapaso permanente. Su autopsia reveló un infarto agudo del miocardio y una enterocolitis necrotizante. Seis pacientes están vivos y relativamente asintomáticos.

Creemos que los resultados obtenidos con el uso temporero de marcapasos eléctricos endovenosos han sido provechosos y estimulantes pues pudimos controlar los síntomas debidos al bloqueo atrioventricular hasta el momento en que fue implantado un marcapasos permanente o que el bloqueo desapareció.

Acknowledgment

We wish to thank Dr. J. E. Lugo, Dr. C. E. Girod, Dr. J. E. López, Dr. S. Padilla and other members of the cardiology department of the University Hospital who have been involved in the placement of the pacemakers.

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TOXICOLOGY OF MERCURY

Sidney Kaye, PhD

Mercury (quick silver) was known to the early alchemists. It has been used and is still used in many industries and in medicine. Mercury, the unusual liquid metal has always been fascinating to look at, and to play with. Unbeknown to many, it can be quite toxic even in its elemental form. Of course, in its more solube state as a salt, it is more acutely toxic.

Occasionally an oral or rectal thermometer is broken in the mouth or rectum; here the danger is minimal once the glass fragments are removed. But metallic mercury spilled in the laboratory, the dentist's office, or played or worked with carelessly can be dangerous after a period of inhalation. Metallic mercury gives off vapors slowly; perhaps not much, but these, after a period of continuous exposure can reach dangerous proportions (*i.e.*, spilled on rugs, corners and crevices, or continuous handling).

The following brief resumé on the toxicology of mercury is offered so that we can be more fully aware of its dangers.

Derivatives and Properties

Derivatives:

Bichloride of mercury (corrosive sublimate) is the most common (blue coffin shaped tablet); mercuric cyanide or nitrate, organic antiseptics (merthiolate: sodium ethyl mercuri thio salicylate), organic mercurial diuretics.

Uses:

Disinfectant, antiseptics, diuretics, antiluetics, amalgams (dentistry), catharties (calomel), insecticides ($HgCl_2$ especially for ants), antifungicide (ethyl mercury phosphate, phenyl mercury acetate, methyl or other alkyl), bivalent mercury compounds are used to preserve seeds, grains, wood, plastics and papers. It is also found in laboratory instruments (manometers, barometers, thermometers), paints, preserving specimens, fingerprint photography (police), treating furs, and "Hatters" felt hats, dry cell batteries, mercury solder, fulmonate for detonators in bombs.

Properties:

Metallic mercury is liquid, silvery, heavy globule, insoluble, but can vaporize sufficiently at room temperature to reach, in time, toxic levels. $HgCl_2$ is a very corrosive, white crystalline salt, sparingly solube in water (1:13). Organic bivalent mercury compounds are also very volatile and can be absorbed through all portals including skin and are strong skin irritants.

MLD:

Approximately 500 mg for a 150 lb man

From the Department of Pharmacology and the Institute of Legal Medicine, School of Medicine, University of Puerto Rico.

($HgCl_2$). Other inorganic mercury compounds vary in toxicity depending upon their solubility. Organic mercury compounds vary widely. Phenyl mercuric salts or esters are almost as toxic as $HgCl_2$, but are less corrosive.

Remarks:

Known since the lst. Century. There is no beneficial use in man. It is not a normal trace element in man. Normal levels are zero to about 15 ug in 100 ml blood or 1000 ml urine, depending upon the person's occupation. Exposure may occur by all portals including the inhalation of metallic vapors. If exposure is low grade and chronic, kidney will eliminate mercury in urinc for many months after last exposure without any apparent damage.

Acute Intoxication

In the acute phase symptoms are produced within minutes of exposure. Very quickly there is a sensation of burning in the mouth and throat, nausea, vomiting, (corrosion) eschars on mouth and lips (ash gray), severe gastro-intestinal irritation, severe abdominal pain, profuse vomiting, and diarrhea, extreme thirst, and salivation, loss of fluids and electrolytes, rapid weak pulse, pallor, cold moist skin and slow breathing. Shock, peripheral vascular collapse and death may follow. If much vomiting occurs and fluids are replaced, the patient may survive for several days and even recover if the absorbed mercury compound is less than 500 mg.

Delayed actions are evident after about 12 hours to several days. The lower bowel is injured more than the stomach. Ulcerative coliti develops in about 24 hours. Salivary gland swelling, stomatitis, excessive salivation, metallic taste, foul breath, soft spongy gums, loose teeth, blue-black gum line (sulfhydryl) may occur. Initially the urine volume increases, later there is oliguria, anuria, uremia and acidosis. There is renal tubular necrosis. Central necrosis of the liver is possible. Death is usually due to renal failure.

Chronic Intoxication

Exposure may be by all portals of entry including the breathing of metallic mercury which vaporizes sufficiently at room temperature to be dangerous. Brushing of mercury salts on to furs or hats is a well known form of exposure ("Mad Hatter"). Dentists, laboratory researches (thermometer or manometers), workers in industry may be exposed. Usually low grade but continuous exposures may bring the following symptoms and signs: inflammation of the mouth, swollen salivary glands, soft spongy gums, loose teeth, blue-black gum linc, excessive salivation, metallic taste, foul breath and muscular tremors.

Trembling occurs when patient knows that he is observed and it stops during sleep or when not being observed. This has been called "hatters shakes". On an accustomed job, he does fine, but under pressure, observation or in a new job he will violently shake. As it develops and gets worse, tremors spread to the arms and legs.

Behavioral changes (Kussmaul called it "Erythismus mercurialis") include: stammering, shyness, anxiety, restlessness, insomnia, loss of self confidence, fear of losing job, loss of concentration and memory, loss of drive, energy or interest, forgetfulness, melancholia.

With low grade exposure excretion of small amounts of urinary mercury may go for a long time without any apparent kidney damage.

With an increased regular exposure, the above symptoms are intensified. The cumulation of mercury now begins to approach early symptoms of the acute phase as the tissue mercury level increases. Kidney damage and severe colitis

may appear.

Mental and nervous symptoms are rare in the single acute phase except in the case of exposure to organic mercurial compounds used in agriculture (alkyl mercuric salts or phenyl mercuric derivatives) which produce prompt and marked nervous symptoms such as ataxia, visual disturbances, paresis, delirium. These, although alarming, may be surprisingly transient.

Sometimes there is a hypersensitivity to organic mercurial diuretics leading to renal failure.

Identification

Reinsch Method:

Place a small strip of clean copper sheet (about 5 x 10 mm) into 20 ml of urine, gastric contents, vomitus, ground homogenate of kidney or liver, then add 5 ml of hydrochloric acid and *gently* heat in a suitable size Erlenmeyer flask for about one hour. Heat gently and try to maintain volume with a watch glass on top. If mercury is present (sensitivity about 0.030 mg), the copper strip will be "silver" coated. This "silver" coating can be estimated fairly well in ranges 0.05, 0.10, 0.15, 0.25 mg/20 ml by visual inspection.

This silvery deposit can be specifically confirmed by placing the copper and deposit on a piece of filter paper and then overlaying several drops of a suspension of cuprous iodide. Cover with a watch glass and within 1-2 hours a distinct salmon pink indicates mercury (HgI_2) method is sensitive to about 0.020 mg. The intensity and distribution of this pink color is proportional to the quantity of mercury on the copper strip.

The cuprous iodide reagent is prepared as follows: dissolve 5 g of $CuSO_4$ and 3 gm of $FeSO_4$ in 10 ml of water. Seven grams of KI in 50 ml of water is then slowly added while stirring. Allow to stand and settle and then decant. Wash the settled precipitated (Cu_2I_2) with small amounts of water and again carefully decant. Repeat until the washings are relatively free of excess iodine (yellow washings). The light tan Cu_2I_2 is then transferred with minimal water (to make a suspension) to a small brown bottle with a tight stopper. This is used in the form of drops or emulsion.

Dithizone Methods:

These methods are more sensitive and reliable, being sensitive to 0.002 mg of mercury.

Walls and Rhodes' method (1):

Fifty ml of urine is gently digested with 10 ml of 50 percent v/v sulfuric acid and 3 gm of potassium permanganate in a 500 ml Erlenmeyer flask. The flask is covered with a watch glass and the contents are allowed to gently simmer on a hot plate for about 30 minutes. If the $KMnO_4$ is completely decolorized, more is added.

Sufficient hydroxylamine hydrochloride (50 percent) is now slowly added to the warm solution to dissolve the precipitated manganese dioxide, and to destroy free oxidizing material, then a few drops is added in excess. About 3 ml usually suffices. The digested solution is now colorless or faint yellow.

Cool to room temperature and transfer to a separatory funnel. Test with KI starch paper to be certain that all oxidants are absent. Extract with 10 ml of dithizone solution (10 mg/liter CCl_4) for about 30 seconds. Separate and save. When mercury is present in large amounts, this first 10 ml extraction is peach colored. If only a few micrograms of mercury are present, the dithizone in the first extract remains green and further extraction is unnecessary. Read this in the spectrophotometer nonetheless, to establish that they are only trace amounts.

If serial 10 ml extractions are required, each dithizone extract is kept separate and the extraction is repeated, each with another 10 ml of dithizone until finally a *persistent green* remains.

Each separate 10 ml extract is read at 490 mμ in a 1 cm cuvet with dithizone solution as the reference standard. Add all values for total. Report output per 24 hours.

If the maximum density above is read at 390 mμ, (oxidized dithizone is yellow), and not 490 mμ (mercury dithizone is peach yellow), then re-analyze, this time be certain that all oxidizing agents are removed.

Standardization is made with mercury standards of 2 to 10 μg which were digested in an identical manner.

Copper may sometimes (but rarely) interfere. This is indicated if the dithizone extract is red instead of peach, yellow, or green. If copper is present, add 75 ml of de-ionized water, 2 ml of 50 percent (v/v) sulfuric acid, and 4 ml of 1.5 percent (w/v) sodium thiosulfate, to the combined dithizone

extraets. Shake for about 1 minute and then discard the carbon tetrachloride (lower) layer. The aqueous is transferred to an Erlenmeyer flask and simmer with 0.3 g of potassium permanganate for about 10 minutes. Then continue to decolorize and continue as above.

Natelson's method (2):

Reagents:

1. Dithizone: 25 Mg/liter of redistilled chloroform. Dilute 1:2 before use with redistilled $CHCl_3$.

2. Hydroxylamine. HCl: 50 g in 50 ml of H_2O purify (delead with dithizone).

3. Ammonium hydroxide (9N): 100 ml NH_4OH +60 ml H_2O. All distilled water redistilled thru pyrex glass apparatus. Copper is most common interference (especially in the HNO_3). Fisher reagents have been low in copper.

Procedure:

To 10 ml * of urine in an Erlenmeyer flask, while cooling under top water, add 1 ml of sulfuric acid. Mix and add 2 ml of nitric acid. Place a watch glass as a lid then mix and then heat gently to barely a simmer for about 5 minutes. Remove from heat and add 5 ml of potassium permanganase (5 percent) a little at a time to minimize foaming. MnO_2 will start to precipitate out. When all is added, heat gently again with a watch glass lid for about 10 minutes at barely simmering. Swirl gently from time to time.

Allow to cool to room temperature then add 3 ml of hydroxylamine reagent in small portions to dissolve the MnO_2 and to remove excess oxidizing agents. Now test for absence of oxidizing agents with KI starch paper (colorless). Transfer to a small Pyrex separatory funnel and shake with 5 ml of carbon tetrachloride to remove fats. Continue on to extraction with dithizone without delay. First make certain that pH is below 2(1-2). Adjust if necessary with dilute NH_4OH or H_2SO_4 (as required) using pH test paper.

Add 5 ml of dithizone dilute solution (1:2) and shake extract vigorously. Yellow to peach-orange indicates mercury. Settle, separate and collect the bottom dithizone extracts. Add an additional 5 ml of dithizone and again shake-extract vigorously. Settle, combine and collect extracts. Repeat with another 5 ml if necessary until all the mercury is extracted as is indicated by a final persistent green dithizone. Calculate how much dithizone was required to reach this point. All the combined dithizone extracts are now shaken with 25 ml of NH_4OH(9N) to remove excess dithizone.

Quickly separate and filter the dithizone through filter paper to remove droplets of water.

Read at 490 mμ in a spectrophotometer, with a dithizone reference blank.

To rule out possible bismuth interference, add 50 mg of potassium cyanide to the residual NH_4OH (9N) and return a sample of the mercury-dithizone and shake. The color will instantly disappear. If bismuth is present, the orange color will persist.

Using 10 ml of urine and if only (One) 5 ml of dithizone was required, with a Beekman DK-2A recording spectrophotometer and a 10 mm light path, the following o.d. was obtained:

Hg	Optical density
4 μg	0.130
8 μg	0.270
12 μg	0.390

Diphenyl Carbazone method:

S diphenyl carbazone (EK number 4459) 100 mg dissolved in 100 ml of 95 percent ethanol.

Ten ml of filtered stomach contents or residue plus 1 ml of S diphenyl carbazone produces an intense blue color with even traces of mercury (presumptive).

Treatment

Vomiting helps to remove some of the poison quickly. Syrup of ipecac may be used to stimulate vomiting. Gastric lavage (if early) with milk, water, or water and sodium formaldehyde sulfoxalate may be effective. Egg white, milk and cream or albumin are good demulcents, Morphine is used for pain. Atropine may be used to help control excessive salivation; alkaline fluids ($NaHCO_3$), to correct acidosis. Maintain body heat, electrolytes and fluid balance. Keep alert for shock and early signs of kidney involvement.

BAL is the specific antidote for the acute phase. Intramuscular doses are slightly higher

** If only a trace of mercury is suspected, digest 50 ml of urine.*

than used for arsenic. Initial dose is usually 4 mg/kg. Continue every 6 hours with 3 mg/kg for two days. On the third day continue with 2 mg/kg for 3 more days. Evaluate the patient. Analyze urine for mercury levels and if levels are still high give another 2 mg/kg series for 5 days.

BAL has an objectional odor, and is painful on injection. It may also give side reactions. Antihistamine treatment prior to BAL may help minimize the side reactions of this drug.

D-1 penicillamine has also been used in mercury poisoning with good results. It can be given orally.

Hemodialysis is indicated for renal insufficiency even though it is ineffective in removing any appreciable amounts of mercury. Prognosis is poor if there is oliguria.

Organic Mercury Compounds

Bivalent organic mercury compounds are usually used as fugicides. Alkyl (methyl or ethyl or methoxy, etc.) or Aryl (phenyl or Tolyl etc.) which is combined with an organic acid; for example, ethyl mercury phosphate or phenyl mercury acetate. These compounds are used to preserve seeds, grains, vegetables, cotton, fruits, and wood.

They are absorbed through all portals — skin absorbed and inhalation (highly volatile). They are strong skin irritants (blisters) and are highly toxic in any form.

Symptoms are roughly similar to inorganic mercury except that the gastrointestinal symptoms are rare. Nervous symptoms are predominant but may be delayed even months after exposure. Tremors, loss of coordination and peripheral vision, noticeable effect on speech, writing, walking and standing may be present.

Treatment is uncertain. BAL is of questionable value (may even be harmful). EDTA has been reported to be of some help.

Summary

Chronic mercury poisoning is an insidious disease. The clinical diagnosis is not easy; signs and symptoms and the clinical picture should be correlated and confirmed with mercury determinations in urine.

Common signs and symptoms are described and several standard chemical methods are given. Modification of the Reinsch test is included because of its simplicity, and the dithizone technic for its sensitivity.

For the acute phase of this poisoning, BAL is an excellent antidote and can be life saving. It may be contraindicated in chronic cases.

The risk of mercury poisoning is ever present in our society and the physician should always be on the alert to its possibility.

Resumen

La intoxicación crónica con mercurio es una condición insidiosa. El diagnóstico clínico no es fácil ya que los síntomas y signos son generales y vagos. La determinación de mercurio en la orina, correlacionada con el cuadro clínico es necesario para poder llegar a un diagnóstico final.

Se describen varios métodos para la determinación de mercurio; la modificación del método de Reinsch se incluye por su sencillez y el dithizone por su sensitividad.

En la fase aguda de la intoxicación con mercurio, BAL es un antídoto excelente; en la fase crónica está contraindicado.

El envenenamiento con mercurio es una eventualidad que debe tenerse en mente en una sociedad moderna; los médicos deben estar siempre alerta de la posibilidad de esta condición.

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A QUIEN MUCHO SE LE DA, MUCHO SE LE RECLAMARA

J. A. Alvarez de Choudens, MD

Hace pocos días presenté a nuestra Cámara de Delegados el informe de la labor que en nombre de nuestra Asociación tratamos de haeer en el año que llega a su término. Esta noche me dirijo a ustedes por última vez eomo Presidente. Aunque hemos pasado algunos momentos amargos, he disfrutado este año y quiero expresarles mi hondo sentimiento de gratitud por la oportunidad que me dispensaron de servirles desde la presidencia.

Hemos reeonocido ya la eolaboraeión de algunas personas que en forma espeeial trabajaron por nuestra asociación; son muehas las personas médicos y no médicos, aquí presentes y también ausentes que merecen nuestro profundo agradeeimiento. Entre éstos se distingue nuestro sobresaliente Presidente Entrante. Especial agradecimiento merecen esas personas objeto de nuestro afecto, respeto y cariño que con sus horas de soledad, sacrificio, paciencia, dedicación y colaboración hacen posible nuestra dedicación a la Asociación, nuestra misión como médicos. Al saludar a mi esposa, Ligia, saludo en vuestro nombre a todas nuestras esposas. Y aprovecho esta oportunidad para ofrecerle un momento de agradeeimiento a una persona que nutrió en mí el ideal de dediear mi vida al servicio de mis hermanos, mi Mamá. Al saludarla a ella saludo en vuestro nombre a las madres de los médicos de Puerto Rieo.

La asociación voluntaria de dos seres humanos, uno buscando y el otro ofreeiendo alivio, es el alma del arte de la medicina.

La necesidad de esta asociaeión no surge de la voluntad del doliente, no se enferma éste porque así lo desee.

El médico sí acepta voluntariamente la misión de aliviar los males del afligido al reconocer una llamada a servir a su prójimo. Al haeerse médico asumió serias obligaciones haeia sus pacientes. Estas han sido expresadas en la "Deelaración de Ginebra" de la Asociación Médica Mundial eomo sigue: "Solemnemente me eomprometo a consagrar mi vida al servieio de la humanidad". "Mi principal preocupación será la salud de mis paeientes".

El reeonoeimiento de estas obligaciones fue la fuerza ereadora de los códigos de ética médica. El más antiguo existente, conocido eomo el Código de Hammurabi, fue còncebido en Babilonia alrededor del año 2500 AC. En este antiguo código se exponía en detalle la eonducta que se esperaba del médico. El juramento de Hipóerates nos ha llegado del Siglo V AC como una expresión viva y práctiea de los ideales que debería honrar el médico. Esta corta exposición de principios protegía los dereehos del enfermo y apelaba a los mejores instintos y sentimientos del médico. A través de los siglos ha perdurado como expresión de la conducta ideal del médico de la civilizaeión occidental.

La Asociaeión Médica Americana estableció

**-Discurso presidencial pronunciado el 12 de noviembre de 1968 durante la Sesión Inaugural de la Sexagésima Sexta Asamblea Anual - Hotel San Juan, San Juan, Puerto Rico*

en 1847, un código de Etica Médica, cuyos conceptos básicos no han variado hasta nuestros días. Las revisiones periódicas resultaron en un documento cada vez más complicado que para el 1955 contenía cuarenta y ocho secciones. En el año 1957 la AMA aprobó un código simplificado de diez secciones el cual es la base del código de la AMPR.

Algunas de las secciones de nuestro código de ética leen como sigue:

Sección 1 - El objetivo principal de la profesión médica es rendir servicios a la humanidad con máximo respeto a la dignidad del ser humano.

Sección 4 - La profesión médica debe salvaguardar tanto al público como a sí misma, de aquellos médicos de dudosa conducta moral o competencia médica. Los médicos deben obedecer todas las leyes, proteger la dignidad y honor de la profesión y aceptar las disciplinas auto-impuestas. Deben denunciar sin vacilación la conducta ilegal o falta de ética de cualquier otro miembro de la profesión.

Sección 6 - El médico no debe disponer de sus servicios bajo términos o condiciones que tiendan a interferir con o impidan el libre y completo uso de su destreza y juicio médico, o que tiendan a causar un deterioro de la calidad del cuidado médico.

En nuestro deseo de cumplir con nuestra misión como se expresa en nuestro código de ética debemos velar siempre porque no se debilite la piedra angular del arte de la medicina, que lo es "la asociación voluntaria de dos seres humanos, uno buscando y el otro ofreciendo alivio". La defensa de este principio que hemos llamado "el sagrado derecho del paciente a escoger libremente al médico de su fe", merece la dedicación completa de todo médico. Tiene que continuar nuestro empeño por conseguir que todo puertorriqueño pueda hacer uso del derecho a escoger libremente a su médico para que así tome verdadero significado el apelativo M.D., que prefiero leer como Mi Doctor.

Permítanme presentar aquí una opinión que no puedo respaldar con estadísticas. Estoy convencido de que he sido mejor médico al estar consciente de que sólo soy instrumento de Dios y al dedicar todos mis actos a servirle a El sirviéndole a mis hermanos. Creo que el médico más inteligente, mejor preparado, y de mayor experiencia en el mundo sería un mejor médico si en su práctica se rigiera por el mandamiento "amaos los unos a los otros como os he amado Yo".

Y permítanme presentar una segunda opinión que tampoco puedo respaldar con estadísticas. Creo que el tener creencias religiosas bien fundadas equipa a las personas para bregar con las situaciones desfavorables de la vida, las protege de las tensiones, y ansiedades del diario vivir. Tengo el convencimiento que mis pacientes auténticamente religiosos gozan (en igualdad de condiciones) de las siguientes ventajas: Toleran mejor los embates de la vida, evalúan más objetivamente sus problemas de salud, establecen mejores relaciones con el médico, entienden y siguen las instrucciones del médico con mayor exactitud, se enfrentan mejor a las complicaciones médicas que puedan surgir, y hacen con mayor éxito los reajustes de vida que la dolencia pueda requerir.

Hasta aquí hemos hablado de la relación del médico con su paciente. Las primeras nueve secciones de nuestro código se refieren a esta relación.

La sección 10 de nuestro código dice: "Los ideales de la profesión médica implican que las responsabilidades del médico se extienden, no sólo a la persona, sino también a la sociedad donde su misión incluye el interés y participación en actividades con el propósito de mejorar tanto la salud como el bienestar general de la persona y de la comunidad.

En la misión que nos impone esta sección,

con frecuencia nos encontramos insuficientemente preparados ya que en este aspecto recibimos poco entrenamiento. En nuestro tiempo, los cambios sociales y económicos y los acelerados avances en la medicina imponen cambios en las estructuras de los servicios médicos que permitan la más rápida y eficiente aplicación de los nuevos conocimientos. El aumento en espiral de los costos en los servicios de hospital, causados en gran parte por la aplicación de los adelantos científicos, es un importante problema de nuestra época.

Como médicos tenemos que tomar la delantera y con la cooperación de los otros grupos del equipo de la salud, resolver éste y los otros muchos problemas que existen en nuestro sistema doble de salud. Pero nuestro afán de resolver problemas no debe llevarnos nunca a aceptar "disponer de nuestros servicios bajo condiciones que puedan tender a interferir con o impedir el libre y completo ejercicio de nuestra destreza o juicio médico o pueda causar un deterioro de la calidad del cuidado médico".

Y cuando exista la duda, debemos consultar a nuestro comité de ética.

Hace falta vigoroso liderato en salud. Los serios problemas existentes demandan acción vigorosa y rápida. Solamente nosotros, los del equipo de la salud, poseemos los conocimientos que pueden llevar a la solución correcta de estos problemas. Nuestro pueblo no puede esperar mucho por las soluciones, y de no proveerlas los *eruditos* en salud, surgirán irremediablemente propuestas mal orientadas, basadas en conocimientos insuficientes, pero fruto de la desesperación ante el problema inadecuadamente atendido.

"A quien mucho se le dá, mucho se le reclamará, y a quien mucho se le ha entregado mucho se le pedirá". He citado el Evangelio según San Lucas quien también fue médico.

Como médicos hemos recibido mucho y por eso de nosotros, mucho se reclama.

Dios nos ha dado el privilegio de vivir en un país que no importa sus defectos nos ofrece un grado de libertad de acción, libertad de pensamiento, libertad de expresión, libertad de credo, libertad para dirigir nuestro destino como pueblo por medio del voto..... no aventajado en ningún sitio en el mundo y no igualado en la mayoría de los pueblos.

El uso responsable de esa libertad ha permitido que nuestro país haya logrado avances extraordinarios en los últimos 28 años. Quiso el Señor que nuestro pueblo optara por un cambio de gobierno en las recientes elecciones escogiendo el partido que había adoptado casi en su totalidad el programa de salud de nuestra Asociación. Esperanzados empezaremos el próximo año esperando la rápida implementación de las medidas de salud prometidas por el nuevo partido de gobierno.

El año al cual nos enfrentaremos requiere sobrio optimismo, determinación, acción creadora, dedicación y espíritu de sacrificio. La motivación de todo médico verdadero, el servicio a la humanidad, tiene en ella la fuerza necesaria para un esfuerzo entusiasta, vigoroso, dedicado y fructuoso.

Los tiempos nuevos requieren el darnos cuenta de la enorme fuerza potencial de recursos en favor del bien que existe dentro de cada médico y dentro de la AMPR que nos une. Y al darnos cuenta de esto, debemos utilizar estas fuerzas hasta el máximo de nuestra potencialidad por el bien de nuestro pueblo.

¡Quiera Dios concedernos que así sea!

CASE REPORT

AMINO-GLUTETHIMIDE (ELIPTEN) IN ADRENOCORTICAL CARCINOMA

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Aminoglutethimide (Elipten) was introduced in 1958 as an anticonvulsant by Ciba Pharmaceutical Corporation. In 1966 Camacho *et al* (1) presented data suggesting that changes in the serum electrolytes and adrenal histology, and clinical manifestations of adrenal insufficiency in children result from the administration of amino-glutethimide (AG). The drug was withdrawn from the market for further evaluation. Studies in humans and animals have demonstrated that AG produces histologic changes in the adrenals which suggest an early block in steroidogenesis with alteration in the pathway of degradation of cortisol (1-8).

AG was shown to be capable of inhibiting cortisol secretion, lowering plasma and urinary 17-hydroxycorticosteroids in a case of adrenal cortical carcinoma with metastases without symptoms of drug toxicity (9). Similar responses have been noted by others in patients with adrenal cortical adenoma and carcinoma (3-11).

The purpose of the present study was to determine whether aminoglutethimide was capable of inhibiting adrenal cortical function in a child with metastatic carcinoma of the adrenal cortex. Secretion rates were not performed in our patient, but we observed significant suppression in the urinary excretion of 17-ketosteroids and Porter-Silber chromogens with associated clinical improvement, arrest of virilization and significant regression of pulmonary metastases while the drug was administered. We consider it unlikely that these changes are related to regression of the neoplasm secondary to radiation, since the pulmonary metastases progressed during and following radiation therapy and the latter was confined to the tumor bed.

Material and Methods

A 2 1/2 year old boy with metastatic adrenal cortical carcinoma received aminoglutethimide after surgical resection of the primary tumor and radiotherapy had been completed. He was hospitalized for the study in the Pediatric Ward at University Hospital and later treatment was continued at home under close medical supervision.

Studies consisted of urinary 17-ketosteroids (17-KS) and 17-OH-corticosteroids (17-OHCS), plasma 17-OH-corticosteroids, serum protein bound iodine, Na, K, CO_2, Cl, blood urea nitrogen, fasting blood sugar, urinalysis, complete blood counts and chest X-rays, skeletal survey and complete physical examinations which were done periodically during the period of observation.

The urinary 17-ketosteroids were determined by the method of Peterson and Pierce (12), the urinary 17-hydroxycorticosteroids by the method of Peterson (13) and the plasma 17-hydroxycorticosteroids by the method of Silber (14). Other laboratory tests were done by accepted methods.

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This work was supported in part by Research Project M-67-34 from the General Medicine Research Fund of the University of Puerto Rico School of Medicine. Elipten® was kindly supplied by Dr. A. R. Flora of the Ciba Pharmaceutical Company; Summit, New Jersey.

Clinical History and Results

The patient developed pubic hair and enlargement of the penis around 15 months of age (April 1966) and at this time his 24 hour urinary 17-ketosteroids were reported as 33.8 mg. He was lost to medical follow-up until January 1967 when urinary 17-ketosteroids of 90.7 mg/24 hr. associated with a progressive spurt of growth and virilization were present. He was first seen by us and admitted to the University Hospital on March 2, 1967 at the age of 2 3/12 years.

Physical examination revealed: B.P. 120/90 mm Hg; weight, 36 lbs.; height, 38 in.; height age, 3 1/2 years. He was tall and muscular with advanced height age and skeletal proportions (Fig. 1). His voice was deep and there was acne of the face and fine short hair over the face, upper lip, around the nipples and axillas. A large firm, non-tender irregular mass was palpable on the left upper abdominal quadrant. The testes measured 1 x 1.5 cm each, the scrotum had well developed rugae and brownish pigmentation which was also present in the perianal area. The penis was easily erectile and 5.5 cm long with a circumference of 6 cm at its base. A moderate amount of curly, thick, brown hair, about 1.5-2 cm long was present over the suprapubic and perianal regions. The prostate gland was not enlarged.

Complete blood count, serum electrolytes, glucose and urinalysis were normal preoperatively. Twenty four hours urinary 17-KS was 90 mg and 17-OHCS was 4.0 mg. X-ray of the abdomen on admission showed the presence of curvilinear calcifications in a chain fashion in the area of the left adrenal gland associated with scattered, discreet calcifications located within a large mass which extended for approximately 3 cm inferiorly and laterally to the left kidney shadow (Fig. 2). Oblique films demonstrated the anterior location of this mass. Chest film on admission showed no parenchymal lesions (Fig. 3). A bone age of the hand was estimated as 3 1/2 years.



Fig. 1: At 2 3/12 years he was tall and muscular with advanced height age and skeletal proportions and signs of virilization.



Fig. 2: Curvilinear calcifications in the left adrenal gland overlying the renal shadow.

Discussion

This case presented with the adrenogenital syndrome and absence of clinical signs of hypercortisolism except for the initial hypertension and mild elevation of urinary 17-OHCS. It is possible that the slight decrease of urinary 17-KS initially observed could have been brought on by partial regression of the tumor due to radiation, however the increasing number of pulmonary metastases observed during and following radiotherapy make it unlikely that the subsequent disappearance of androgenic effects and metastases was related to it. These biochemical and clinical alterations occurred during the course of long term therapy with AG, associated with a normal level of plasma 17-OHCS and sustained suppression of urinary Porter-Silber chromogens and 17-KS, all of which became significantly elevated after cessation of therapy.

Spontaneous remission in patients with Cushing's syndrome due to adrenocortical tumor has been rarely reported (15-19). We are not aware of reports of spontaneous remission of metastatic adrenal tumors. Amino-glutethimide appeared to possess antitumor properties, inasmuch as it was associated with regression of metastatic lesions during the study period.

AG produces a block in the synthesis of adrenal cortical steroids at an early stage in the conversion of cholesterol to pregnenolone. Thus one would expect aldosterone, cortisol and androgens production to be decreased. It would be of interest to study the effect of AG on androgen metabolism. If the drug interferes with the biosynthesis of biologically potent adrenal androgens it may prove valuable in the therapy of conditions associated with an increased production of these hormones. Differences in the excretion pattern of urinary 17-KS were reported by Schteingart *et al* (9) in normal subjects and in patients with Cushing's syndrome which suggested that more than a single locus of action of AG on cortisol biosynthesis exists. Secretion rates would better document the degree of inhibition on adrenal steroidogenesis but unfortunately these were not done in our case.

Dexter, *et al* (4) observed little or no cholesterol accumulation in the adrenals of hypophysectomized rats treated with AG and suggested a block in ACTH action at a step prior to its well known effect in conversion of cholesterol to pregnenolone. They also observed that the normal increase in adrenal venous corticosterone in response to ACTH was abolished in hypophysectomized rats and decreased in intact rats given AG.

An increase in ACTH release in response to an early block in cortisol synthesis induced by AG has been observed with resultant compensatory adrenal stimulation so that cortisol secretion rate (CRS) and plasma 17-OHCS remain normal. There seems to exist an alteration in the peripheral metabolism of cortisol since the urinary 17-OHCS are diminished without a significant decrease of CSR; however, the exact mechanism involved remains unexplained. In patients with autonomously functioning adrenocortical tumors the sharp fall in the CSR and plasma 17-OHCS is apparently the result of total absence of ACTH. In a case of oat cell carcinoma of the lung producing an ACTH-like substance and in some cases of Cushing's syndrome (9) the partial suppression of CSR despite elevation of ACTH levels could have resulted from a relatively fixed ACTH secretion. It has been found with few exceptions that AG (11, 20) does not effectively suppress adrenal cortical function of non-tumorous origin (9).

Givens *et al* (20) treated a case of Cushing's disease with AG and observed adrenal cortical steroids suppression and disappearance of clinical signs of hypercortisolism for seven months after discontinuation of therapy. They concluded that an alteration in the aberrant control

TABLE I: SUMMARY OF LABORATORY STUDIES DURING AMINO-GLUTETHIMIDE THERAPY

Date	Therapy	Hemoglobin g percent	WBC per mm^3	DIFFERENTIAL Percent		SERUM mEq/L Na	K	CO_2	Cl	BUN mg percent	Glucose mg percent	PBI mcg percent	BONE AGE years
3/3/67	None	10.8	13,500	Seg 36 Lymph 59 Mono 2	Stab-2 Baso-1	142.0	4.9	20.8	101.9	-	52.0	-	3 1/2
5/3/67	Radiotherapy	12.0	9,409	Seg 17 Lymph 81 Stab 1	Eos-1	-	-	-	-	-	-	-	-
6/17/67	None	11.3	7,707	Seg 52 Lymph 43 Mono 5		139.0	5.0	20.6	110.0	13.0	53.0	-	4
6/23/67	AG 250 mg/day	10.8	8,644	Seg 56 Lymph 29 Mono 10	Eos-5	132.0	5.0	25.0	-	-	93.0	-	-
7/1/67	AG 250 mg/day	11.4	6,777	Seg 48 Lymph 50 Mono 1	Eos-1	140.0	6.4	25.5	99.0	6.0	79.0	-	-
7/6/67	AG 250 mg/day	11.4	17,444	Seg 51 Lymph 40 Mono 5	Stab-4	141.0	5.0	23.0	101.0	-	88.0	-	-
7/28/68	AG 750 mg/day	11.7	17,800	Seg 46 Lymph 47 Mono 4	Stab-1 Eos-2	142.0	4.9	21.5	96.0	-	-	5.3	-
10/27/67	AG 500 mg/day	12.7	14,667	Seg 43 Lymph 57		138.0	4.6	23.0	102.0	13.0	70.0	-	-
1/23/67	None for 2 weeks	12.0	13,176	Seg 46 Lymph 53 Eos 1		139.5	4.9	18.9	103.0	-	-	6.2	5

a total dose of 4000 R to the tumor bed because of the appearance of progressive signs of virilization and elevation of the urinary 17-KS to 4.9 mg/day. Chest films on June 6, 1967 showed the appearance of multiple nodular lesions in both lung fields which were more numerous in the right lung (Fig. 7).



Fig. 7: Multiple nodular lesions in both lungs fields, more numerous in the right lung.

He received AG from June 18, 1967 to January 9, 1968 for a total duration of therapy of 205 days. Fig. 8 depicts the steroids pattern during AG therapy. There was a significant decrease in the urinary excretion of 17-ketosteroids and Porter-Silber chromogens which lasted as long as the drug was administered. Plasma 17-OH-corticosteroids level was normal while on AG but rose after cessation of therapy. Table I presents a summary of laboratory studies during long term therapy with AG. There was no significant change in the serum electrolytes, blood urea nitrogen, fasting blood sugar, serum protein bound iodine, or hemoglobin. Elevation of the white blood cell count with normal differential in the absence of detectable infection was present. An increment of 1.5 inches in height and 1 year in osseous maturation was noted. Appetite, weight and spontaneous activity improved and blood pressure remained within normal limits. Slow clearing of the acne was noted and by November 1967 it had completely disappeared with no further growth of the penis, of pubic hair or other signs of virilization, hypothyroidism, goiter, skin pigmentation, rash, weakness or salt craving. No abdominal masses or visceromegaly has been detected. Review of multiple chest films showed that on July 20, 1967 metastases were more numerous bilaterally. On December 8, 1967 and again on January 23, 1968 (Fig. 9) there was no radiographic evidence of metastatic disease in the left lung and almost complete disappearance of the nodules in the right lung except for one well defined lesion located in the sixth intercostal space posteriorly along the midclavicular line, which had been present since June 6, 1967 and had maintained its relative size. Serial skeletal surveys have failed to reveal the presence of bone metastases.

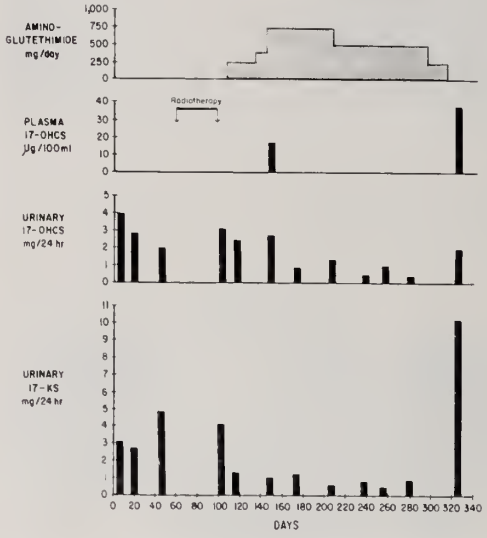


Fig. 8: Steroids pattern during Elipten therapy.



Fig. 9: Chest X-ray reveals one well defined lesion located in the sixth intercostal space along the midclavicular line and no metastases in the left lung.

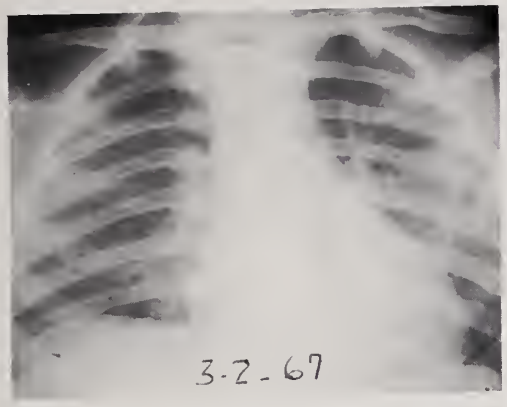


Fig. 3: Chest film at the time of surgery showed no parenchymal lesions.



Fig. 4: Adrenal tumor consisted of a large encapsulated mass which measured 11 cm in diameter and weighed 590 gm.



Fig. 5: Focal invasion of the capsule by tumor cells. (X100)

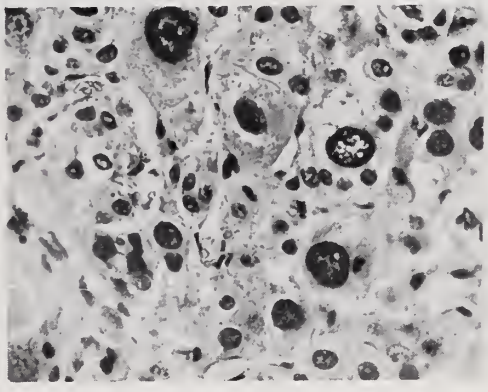


Fig. 6: Tumor composed of large round, and polygonal cells with eosinophilic cytoplasm resembling adrenal cortical cells. (X400)

On March 4, 1967 a large encapsulated mass which measured 11 cm in diameter and weighed 590 g (Fig. 4) was removed through a transverse abdominal incision. A left nephrectomy, splenectomy, and distal pancreatectomy with preaortic lymph node dissection was performed. The tumor showed extensive areas of necrosis and focal invasion of the capsule (Fig. 5). Remnants of the adrenal gland were not readily recognized. It was composed of large round and polygonal cells with eosinophilic cytoplasm resembling adrenal cortical cells, and marked vascularization with a prominent sinusoidal pattern consistent with a diagnosis of carcinoma of the left adrenal cortex (Fig. 6). The kidney, spleen, tail of the pancreas, preaortic lymph nodes and adjacent fat were negative for metastases. The contralateral adrenal was noted to be small in size.

On discharge on March 27, 1967 the patient weighed 33.5 lbs., blood pressure was normal, there was less acne, no regrowth of pubic hair and 24 hours urinary 17-KS were 2.7 mg. Chest film on April 26, 1967 revealed a suspicious metastatic area in the left base which was corroborated with spot films. From May 2 to June 8, 1967 he received

of ACTH characteristic of this condition had taken place since the patient failed to respond to metopirone block but responded to ACTH, synthetic lysine vasopressin and had a normal dexamethasone suppression of her adrenocortical function.

Schteingart *et al* (9) treated a case of metastatic adrenocortical carcinoma with Cushing's syndrome with AG for several months and observed no symptoms of drug toxicity, regression of clinical and biochemical evidence of Cushing's syndrome, apparent arrest of tumor growth and decrease of plasma 17-OHCS, cortisol secretion and turnover rates. In normal subjects and in cases of Cushing's syndrome and primary aldosteronism (3, 9) the most consistent effect of AG was a decrease in the aldosterone secretory rate accompanied by sodium diuresis, decrease in urinary potassium, elevation of plasma renin and some lowering of blood pressure in hypertensive patients. The results of chemotherapy in the treatment of adrenocortical carcinoma have been disappointing. Similarities between amphenone and AG in the inhibition of the conversion of cholesterol to pregnenolone in the rat and bovine adrenal have been demonstrated (21, 22).

The following adverse reactions to AG have been reported (23-27): skin rash, minor central nervous system symptoms, gastrointestinal disturbances and leukopenia. Goitrous hypothyroidism secondary to a block in organification of iodide was identified in three children and demonstrated in rats receiving the drug, with recovery of thyroid function upon its withdrawal (28). AG is structurally related to the aminobenzene derivatives which possess anti-thyroidal properties.

We conclude that from the clinical and radiological findings AG therapy was associated with considerable regression of the pulmonary metastases, on a daily dose as low as 250 mg, without toxic effects or signs of adrenal insufficiency in a boy with adrenocortical carcinoma, and that the effect of the drug on the urinary excretion of 17-KS and 17-OHCS is rapidly reversible.

Summary

The case of a boy with left adrenocortical carcinoma who underwent surgical excision of the tumor and radiotherapy with poor results is presented. Subsequently he received aminoglutethimide therapy for a prolonged period with significant regression of the pulmonary metastases, improvement in the clinical status and arrest of virilization. No side reactions to the drug were observed.

Resumen

Se presenta el caso de un niño con carcinoma de la corteza suprarenal izquierda, cuyo tumor fue removido quirúrgicamente y luego tratado con radioterapia con resultados pobres. Más tarde recibió "Amino-glutethimide" por un largo período, asociado a mejoría en el cuadro clínico, arresto de signos de virilización y regresión significativa de las metástasis pulmonares. No se observaron reacciones tóxicas secundarias a la droga.

Acknowledgment

We wish to express our thanks to Dr. Juan Velázquez and Mr. Antonio Pura of the Department of Pathology of the University of Puerto Rico School of Medicine, and Miss Blanca Jiménez for their assistance in this study, and to Dr. Larry J. Miller and Mr. Nathan Leopold from Castañer Hospital for referring the patient.

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INFORME DE CASO

FISTULA TRAQUEOESOFAGICA CONGENITA TIPO-H

Repaso de la Literatura

H. Arroyo Scotoliff, MD

Dentro de la patología del esófago, cabe destacar por su rareza, las fístulas traqueoesofágicas, que constituyen del 3 al 4 porciento de las anomalías del esófago superior (1), y el 2 porciento de las traqueoesofágicas (2).

En 1873, Lamb (3) y Tarnier (4) aportaron las dos primeras observaciones de esta anomalía, siendo el de Lamb el primer caso dentro de la literatura norteamericana, en un infante de siete semanas de nacido.

Al describir este caso, expondremos los síntomas y diagnóstico de dicha anomalía, conjuntamente con un repaso de la literatura médica referente a la misma (Tabla I) (3-64).

Presentación del Caso

El paciente, un niño, último de cuatro hermanos varones, de nueve, cinco, y dos años de edad, nacido de padres sanos en el Hospital de Distrito de Fajardo el 2 de noviembre de 1966, trás una gestación a término sin complicación de toxemia, ni de polihidramnios. Pesó al nacer 3.402 g, talla 50 cm, siendo dado de alta en la sala de recién nacidos 24 horas más tarde, en buen estado de salud.

Hay que constatar dentro de los antecedentes familiares la existencia de diabetes mellitus y enfermedad cardíaca en la abuela paterna. Por la línea materna, la abuela padeció de enfermedad mental indeterminada, y el segundo de sus hermanos, de asma bronquial.

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A los pocos días de nacido comenzó a presentar episodios de tos relacionados con la ingesta de la lactancia artificial, por lo cual, fue llevado a los médicos de su localidad en tres ocasiones diferentes, siendo tratado con medicamentos para la tos y antibioterapia. Estos accesos, acompañados de cianosis, llegaron a ser tan frecuentes, que en los días precedentes a su hospitalización, su alimentación disminuyó hasta el punto, que solamente podía tomar media onza de leche evaporada en el período de una hora, motivo por el cual fue admitido a los 40 días de nacido en nuestra sala de Pediatría.

Al ingreso el peso es de 3,515 g, talla 52 cm, perímetro cefálico 36 cm, y perímetro torácico 35 cm. El examen muestra un niño eutrófico sin signos de deshidratación.

Los únicos hallazgos positivos fueron algunos estertores diseminados en la base del hemitorax derecho, pero sin la presencia de aleteo nasal, taquipnea, ni retracciones intercostales. Se observó al mismo tiempo que a la ingesta de líquidos, aún sin presentar dificultad en la succión y en la deglución, se producían accesos de tos de tipo espasmódico (tos tipo coqueluchoide) con inyección en las conjuntivas oculares, cianosis circumoral y retracción supraesternal, imposibilitando la alimentación por boca, por lo que hubo de recurrirse al uso de una sonda nasogástrica. Al verificarse este método de alimentación se comprobó la ausencia de los episodios de tos antes mencionados, de donde se sospechó la existencia de fístula traqueoesofágica (si bien los demás síntomas que la acompañan y describiremos más adelante no se manifestaban), cosa que se corroboró por medio de radiografía tomada mediante ingesta de medio de contraste.

Para el estudio fluoroscópico, trás ingesta de una papilla de sulfato de bario, se emplearon las posiciones oblicua anterior y lateral derecha, identificándose en esta última una pequeña fístula traqueoesofágica en la parte alta del torax (Fig. 1).

Al día siguiente del estudio radiológico, segundo

TABLA I: FISTULAS TRAQUEOESOFAGICAS, REPASO DE LA LITERATURA

Autor	Sexo	Edad	Localización	Vía Operatoria	Resultado	Anomalías Asociadas
Lamb (3)	-	7 semanas	1/2" debajo cricoide	-	Murió	-
Tarnier (4)	♂	2 días	epiglotis	Cervical	-	Comunicación intestino y uretra
Cautley (5)	Seis casos sin descripción					
Stubler (6)	♂	2 días	1.1 cm sobre carina	Torácica	Murió	Agujero oval patente
Lohnes (7)	♂	6 semanas	2.7 cm sobre carina	Torácica	Murió	Abceso pilórico
Imperatori (8)	♂	6 1/2 años	5to. anillo traqueal	Cervical	Vivió	-
Gegenbach *et al* (9)	♀	3 meses	3 cm sobre carina	-	Murió	Coartación de aorta y ducto arterioso
-	♀	10 meses	2-3 cm sobre carina	Cervical	Vivió	-
Haight (1)	♂	4 años	1.5-2 cm sobre carina	Torácica	Vivió	-
Foster *et al* (10)	♂	3 días	-	Torácica	Murió	-
Cardullo (11)	♂	5 días	laringe	Cervical	Murió	Malformaciones cardíacas costo-vertebrales e intestinales
Hollinger (12)	♀	21 meses	tráquea inferior	Cauterizado con OHNa	Vivió	-
Helmsworth *et al* (13)	♀	6 meses	tráquea	Torácica	Vivió	-
Knox (14)	♀	14 días	2 cm sobre carina	Transcervical y gastro-stomía	Vivió	-
Fluss *et al* (15)	♀	8 meses	carina	Torácica	Murió	-
Leight *et al* (16)	♂	6 semanas	1 cm sobre carina	Torácica	Vivió	-
-	♂	1 semana	medio de la traquea	Torácica	Vivió	-
-	♀	3 días	-	Torácica	Murió	-
-	♂	8 días	a nivel D_2	Torácica	Vivió	-
Fergunson (17)	♀	1 mes	a nivel D_2	Torácica	Vivió	Arteria subclavicular derecha anormal
-	♂	10 meses	debajo botón yugular	Torácica	Murió	Mongolismo, arteria subclavicular derecha anormal
-	♀	7-1/2 meses	1-3 cm sobre carina	Torácica	Murió	Uréteres dobles
Roy *et al* (18)	♂	7 meses	-	Cervical	Vivió	-
Robb (19)	-	11 años	mitad de la tráquea	Torácica	Vivió	-
Ware *et al* (20)	♂	46 días	3ra. costilla debajo vena subclavia	Torácica	Vivió	-
Goulston (21)	♂	2 meses	D_1	Torácica Cervical	Vivió	-
-	♂	2 meses	D_1	Cervical	Vivió	-
Wassner (22)	♂	3 años	-	Torácica	Vivió	-
Mathey *et al* (23)	♀	16 años	mitad de tráquea	Torácica	Vivió	-
Petterson (24)	♂	4 años	borde inferior del tiroide	Cervical	-	-
Colt *et al* (25)	♀	22 días	2da. costilla posterior	Torácica	Vivió	-
Pryles *et al* (26)	♀	4 días	1.5 cm debajo cartílago tiroide	No	Murió	Deficiencia sistema ventricular, movilidad del ciego
Schoorl (27)	♀	3 semanas	carina	Torácica	Vivió	-
Herweg *et al* (28)	♀	1 mes	2 cm sobre la carina	Torácica	Vivió	-
-	♀	6 semanas	nivel del ápice	Torácica	Vivió	-
-	♀	23 días	tráquea	Torácica	Vivió	-
Koch *et al* (29)	♂	2 días	debajo de la laringe	Cervical	Murió	Malformaciones arteriales costo-vertebrales y del pulgar derecho
Mallet (30)	♂	7 semanas	2 cm debajo bifurcación tráquea	Torácica	Vivió	-
Sieber *et al* (31)	♀	1 día	-	Torácica	Murió	

-	♀	6 semanas	D_4	Torácica	Vivió	-
-	♀	11 semanas	3 cm sobre carina	Torácica	Vivió	-
Krause *et al* (32)	-	3 días	debajo cartílago cricoide	Cervical	Murió	Atresia bilateral de coanas. Comunicación interauricular.
Turpin *et al* (33)	♀	14 años	orificio superior del torax	Torácica	Vivió	Bronquiectasia. Anomalías costovertebrales.
Babbit (34)	♂	3 días	1. sobre carina 2. debajo de la laringe	Cervical	-	-
Wolf (35)	♀	20 meses	altura bóveda pleural	Torácica	Vivió	-
Haight (36)	-	1 día	-	-	-	-
-	-	2 días	-	-	-	-
-	-	3 días	-	-	-	-
-	-	16 días	-	-	-	-
-	-	18 días	-	-	-	-
Fornara (38)	♂	6 semanas	-	Cervical	Vivió	-
Morse (39)	♂	6 semanas	-	Cervical	Vivió	-
Roberts (40)	Un caso sin descripción.					
Nova (41)	♂	4 días	2 cm sobre carina	-	Vivió	-
Franklin (42)	♂	3 meses	D_2	-	Vivió	-
Miller (43)	♀	2 días	2 cm debajo laringe	Torácica	Murió	-
-	♀	3 días	1.5 cm debajo cuerdas	Torácica	Murió	-
-	♀	3 días	1.5 cm debajo 1ra. costilla; polo inf. tiroide	Cervical	Vivió	-
Triboletti (44)	♂	4 días	-	Cervical y torácica	Murió	-
Fontan *et al* (45)	♀	4 días	-	Torácica	Murió	-
-	♀	2 meses	-	Torácica	Murió	-
Demong (46)	♂	3 días	3 cm encima bifurcación tráquea	Torácica	Murió	-
-	♂	8 años	D_3	Torácica	Vivió	-
-	♂	15 años	D_3	Torácica	Vivió	-
Fabián (47)	♂	-	-	-	-	-
Jaubert (48)	♀	2-1/2 años	-	-	Vivió	-
Fearon (49)	♂	2 días	D_1	-	Vivió	Hernia Hiatal
Roos (50)	♂	2 años	-	-	Vivió	-
Diriart (51)	♂	17 años	1/4 superior de la tráquea	-	Murió	-
Giedion (52)	♀	8 meses	C_5	Cervical	Vivió	-
Pampari *et al* (53)	♂	10 años	-	-	Vivió	-
Moskovitz *et al* (54)	♂	22 meses	-	Torácica	Vivió	-
Bernard (55)	♀	2 meses	D_3 y D_4	Torácica	Vivió	-
-	♂	15 días	-	Torácica	Vivió	-
Goldenburg (56)	♂	1 día	Orificio torácico	Torácica	Murió	-
-	-	-	1.5 cm sobre fístula inferior	Torácica	-	-
-	-	-	-	Torácica	Recurrió	-
Lynn *et al* (57)	♂	3 días	D_1 y D_2	Torácica y gastrostomía	Vivió	-
-	♂	27 días	D_1	Torácica	Vivió	Arteria subclavia derecha aberrante. Anomalías costillas.
-	♂	4 días	3 cm sobre carina	Torácica	Murió	Anomalías de costillas.
-	♂	84 días	C_8	Torácica	Vivió	-

-	♂	64 días	D_1 y D_2	Torácica	Vivió	-
Cornu *et al* (58)	♀	2 años	Debajo de la laringe	Torácica y cervical	Vivió	-
Luomanen (59)	♂	11 meses	Cuerno inferior cartílago tiroideo	-	Vivió	-
Schneider *et al* (60)	♂	4 días	D_1	Torácica	Vivió	-
-	♂	1 mes	D_2	Torácica	Vivió	-
-	♂	2 días	D_1	Cervical	Vivió	-
-	♂	2 meses	D_1	Cervical	Vivió	-
Waterston *et al* (2)	-	3 meses	-	-	Vivió	-
-	-	45 días	-	-	-	-
-	-	74 días	-	-	-	-
Holman *et al* (61)	♂	2 días	-	-	Murió	Trisomía No. 18.
Christiaens *et al* (62)	♂	18 meses	Parte baja, esófago cervical	Cervical	Vivió	-
Roe *et al* (63)	♀	Horas	-	Torácica	Murió	Dos esófagos, comunicación interventricular, agujero oval patente.
Romsdahl *et al* (64)	♀	9 días	-	-	Murió	-
-	-	36 horas	1.5 cm sobre la carina	-	Vivió	-



Fig. 1: Fístula traqueoesofágica "Tipo-II" de localización alta (flecha).

de hospitalización, fue verificada con éxito la intervención quirúrgica (Dr. Raúl T. Justiniano). Después de preparado el campo operatorio, y abierta la cavidad torácica a través de una herida siguiendo el cuarto espacio intercostal derecho, se incidió la pleura mediastínica quedando expuesto el esófago y la tráquea, encontrando que una fístula unía la tráquea con la porción inferior del tercio superior del esófago. Presentaba una trayectoria de delante-atrás y de arriba-abajo inmediatamente por debajo de la vena ázigos. Ligada y seccionada dicha vena, se disecó la fístula en todo su trayecto, siendo seccionada y cerrándose el defecto de la tráquea y esófago con puntos interrumpidos de seda 5-0, dejando un pedazo de esponja de gelatina en las áreas de sutura. A continuación fue suturada la pleura mediastínica, cerrándose por planos la cavidad torácica, habiendo dejado un tubo de toracotomía con drenaje contínuo a una botella bajo agua (water seal). En un segundo tiempo, se realizó una gastrostomía tipo Stamm para alimentar al paciente, que comenzó el segundo día después de operado, siendo removida al sexto, junto con el tubo de toracotomía, trás un post-operario satisfactorio.

El curso ulterior del paciente ha sido normal hasta el momento, presentando un peso de 11.25 kg a los 13 meses de operado, sin haberse producido ninguna sintomatología que hiciese sospechar la posibilidad de reproducirse la fístula.

Comentario

Para explicar la embriología de estas fístulas, debemos recordar que la porción cefálica del intestino primitivo está normalmente partida en un plano frontal por dos repliegues laterales que vienen a unirse en la línea media. Este septum aparece en el embrión de 4 mm, dejando aisladas adelante a las vías aéreas y atrás al esófago. Una anomalía de fusión de los brotes, explica la persistencia de una comunicación entre el esófago y la tráquea (9).

En cuanto a la etiología se han descrito tres teorías para explicar la presencia de fístulas traqueoesofágicas; para unos, sería debida a una deficiente proliferación celular del esófago embrionario, impidiendo una total separación de esófago y tráquea. Otros, como Keith y Spicer (65), opinan, se deba al unirse de forma incompleta los surcos laterales traqueoesofágicos, que normalmente, forman en el embrión un tabique de separación entre la tráquea y el esófago, dando lugar a la aparición de la fístula. Finalmente, hay quienes creen, su causa sea la presión ejercida por anomalías vasculares.

Aparte de las manifestaciones generales de pérdida de peso, deshidratación, apatía, etc., preferimos a este respecto la llamada triada de Helmsworth y Pryles (13), modificada por Herweg y Ogura (28), la cual, consiste en:

1. Episodios paroxísticos de tos relacionados con la ingesta de alimentos, siendo mejor tolerados los sólidos que los líquidos; estos períodos suelen ir acompañados de cianosis.
2. Desaparición de estos accesos tusígenos si se recurre a la alimentación mediante el uso de una sonda nasogástrica.
3. Distensión abdominal durante el llanto, debido al paso del aire traqueal hacia el esófago y de aquí al estómago.

4. Cambios en la auscultación pulmonar de normal a la presencia de estertores, trás la ingesta de alimentos.

5. Neumonitis repetidas secundarias a regurgitación o vómitos de contenido gástrico.

La multiplicidad de los medios de investigación que se han utilizado para este propósito, nos dan idea de las dificultades para encontrar la evidencia de la malformación y al mismo tiempo, la interpretación de los resultados. Ello determina el valor relativo de algunos de estos exámenes aislados.

Para fines diagnósticos se han utilizado los métodos instrumentales y radiológicos, pero estos han sido finalmente suplantados por la radiocinematografía.

Métodos instrumentales: Han sido los primeros utilizados y ponen en evidencia el orificio fistuloso por medio del control endoscópico.

La esofagoscopía tiene el inconveniente de que a veces el orificio de la fístula es tapado por un repliegue mucoso esofágico que dificulta su visibilidad (13).

El método de Herweg-Ogura (28), combina la esofagoscopía y la broncoscopía. La fístula es localizada por la presencia en el esófago de azul de metileno inyectado en la tráquea. Bajo anestesia general, se pasa un tubo endotraqueal cuyo extremo ingerido se sitúa a nivel de las cuerdas vocales, después se introduce un esofagoscopio a la altura del cartílago cricoide, donde se inyecta de 1 a 2 ml de azul de metileno. En caso de fístula el colorante pasa al esófago desde donde se puede ver también el orificio, y luego estudiarse de una forma más precisa por medio de la endoscopía esofágica; la inyección de lipiodol por el cateter combinado a un estudio radiográfico, permite obtener una opacidad de toda la fístula.

Técnica de Prochiantz y Anglade, mencionada por Cornu (58), basada en el aumento progresivo de presión en la tráquea, trás intubación de esta. Al ir retirando lentamente el tubo, aparecen grupos de eructos indicativos del nivel de la fístula, o una dilatación del estómago, con idéntica significación.

La traqueobroncoscopía, modificada por Abbot (66), que hizo preceder el examen endoscópico por la deglución de azul de metileno.

Métodos radiológicos:

Examen global: La deglución oral del producto de contraste no elimina la posibilidad de una falsa ruta laringea, y por consiguiente de una opacidad de la tráquea por vía subglótica. Se ha preconizado la inyección del contraste por una sonda hasta la porción media del esófago (29) o más simplemente por la hipofaringe (28).

Es importante la posición del paciente, tomando en cuenta el trayecto de la fístula; conviene colocarlo en decubito ventral o en posición de oblicuo anterior derecha o izquierda.

Radiocinematografía: Inventada por Jantier (1936), es considerada actualmente como el método de elección para el estudio de la deglución y sus problemas. Una mayor observación a través del amplificador dá una radioscopía de cualidad excepcional y facilita la visión del mínimo pasaje, que la radioscopía "standard" no permitiría identificar. Ofrece como ventajas además, su utilización en el recién nacido por la pequeña dosis de "r" recibida por el enfermo.

En el diagnóstico diferencial vamos a incluir aquellas condiciones que conllevan dificultad en la deglución y cuadros de neumonitis recidivantes, tales como:

a) Atresia de esófago con o sin fístula traqueoesofágica; verificándose su diferenciación al visualizar radiológicamente el material de contraste acumulado en el fondo de saco esofágico.

b) Anillos vasculares, que al oprimir la tráquea, el esófago, o ambos, producen disfagia

y dificultad respiratoria, pudiendo ser observados al realizar esofagogramas y angiocardiogramas.

c) Los divertículos esofágicos faríngeos presentan un cuadro comparable a aquellos que se encuentran en las fístulas esotraqueales sin atresia de esófago; la salivación es muy abundante y existen los accesos de tos acompañados de cianosis y sofocación. La esofagoscopía revela el orificio del divertículo sobre la pared faringea posterior.

d) Fibrosis quística del pancreas, probablemente la causa más común de neumonitis repetidas, diagnosticándose por la prueba del sudor y el historial familiar.

e) Sindrome de Bourton o agamaglobulinemia, con exclusividad en varones y cansante de infecciones pulmonares frecuentes; puede diferenciarse mediante estudios electroforéticos.

f) Disautonomía familiar (sindrome de Riley-Day), al igual que en los casos anteriores, puede llevar adjuntas infiltraciones pulmonares, aparte de ausencia lacrimal, hipotensión postural, alteraciones en las catecolaminas, etc.

El tratamiento de la fístula traqueoesofágica es quirúrgico, consistente en la exposición y ligadura de la misma. En 1939, Imperatori (8), verificó con éxito la primera operación en un niño de seis años y medio de edad, hijo de médico. Siendo a su vez Haight (1), quien primero usó la vía torácica en 1945, en un niño de 5 años que venía siendo alimentado por sonda nasogástrica desde su primer año de nacido. Miller (43) en 1958, verificó el primer caso por la ruta transcervical.

Como anteriormente enumeramos, a causa de la dificultad existente en corroborar el diagnóstico radiológico, algunos autores (13, 46), opinan que ante la sospecha de presencia de esta anomalía, se debe practicar una toracotomía exploratoria sin pérdida de tiempo, para evitar la muerte o daño pulmonar irreversible que pudiera aparecer antes de recurrir al tratamiento quirúrgico.

Summary

A case of tracheoesophageal fistula without atresia of esophagus has been reported.

The embryology, etiology, symptomatology and diverse methods of diagnosis has been discussed.

A review of reported cases in medical literature is included.

Resumen

Hemos presentado un caso de fístula traqueoesofágica sin atresia de esófago. Se discutió su embriología, etiología, sintomatología y los diferentes métodos de diagnóstico usados, juntamente con un repaso de la literatura médica de los casos reportados hasta el presente.

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EDITORIAL

EL AÑO DE LOS LOGROS

Al asumir la presidencia de la Asociación, quiero expresarles que me honra tan alta distinción y espero poder llevar a cabo toda la labor que ustedes desean se realice, tratando de mantener muy alto los postulados y el gran nombre de nuestra Asociación.

Por considerar que me debo a mi Asociación y por creer mi deber llevar adelante sus principios, es que he aceptado este gran honor.

Toda asociación médica tiene dos finalidades importantes: 1. su función social ante los problemas de salud del país; y 2. la protección y defensa de los asociados.

Creo que es responsabilidad del médico contribuir a obtener una mejor salud para nuestro pueblo, crear una imagen pública de hombres de acción, de hombres de servicio, que creemos en nuestra responsabilidad para con la comunidad y estamos dispuestos a aceptarla.

Solamente el conglomerado de obras de cada médico contribuirá a formar la auténtica imagen de la profesión tal como debe conocerla la ciudadanía y tal como debemos legarla a los que esperan ser médicos algún día.

Nuestros esfuerzos estarán dirigidos a tratar de solucionar los problemas y llevar a todas partes la labor que realiza nuestra Asociación y aunando los esfuerzos de todos, lograr la realización de estos objetivos lo que no sería posible sin la ayuda y cooperación de cada médico, ya que la tarea es muy dura y difícil para un solo hombre.

Espero que este año podamos verlo como un Año de Logros para nuestra Asociación y nuestro país.

Hay que aceptar que la salud no es una finalidad del desenvolvimiento económico, sino su base insustituible. La salud es la base para la elevación de los niveles de vida de la sociedad y al elevarse ésta hay una mayor elevación del bienestar de la población y por consiguiente un aumento de la productividad de un pueblo.

La siempre cambiante práctica de la medicina moderna hace que nuestros métodos del pasado tengan que ser adaptados a esos cambios para que nuestra Asociación sea siempre un cuerpo vibrante y dinámico, haciendo así posible una labor fructífera. Solo ocupando nuestro puesto en la comunidad y aunando todos los esfuerzos de nuestra Gran Familia Médica será nuestra voz oída como voz orientadora y experimentada en la lucha por la solución de los problemas de salud.

El diálogo productivo con la comunidad, y con las profesiones afines, podrá llevar adelante los principios de nuestra Asociación y hacer posible el encauzar los cambios

que se presentan ante nuestros ojos por el sendero que lleve a la mejor solución de nuestros problemas médico-hospitalarios.

Esperamos que estos cambios nos conduzcan a programas de salud armónicos con las necesidades de nuestro pueblo para que veamos en un futuro cercano la realización de una libre selección de médico y hospital para todas las clases de nuestra sociedad.

Martín A. Iguina Mora, MD

NOTA BIOGRAFICA

Nació el Dr. Iguina Mora en Arecibo, Puerto Rico, el 1ro. de octubre de 1920. Cursó estudios elementales en su pueblo natal. En 1942 recibió su Bachillerato en Ciencias Agrícolas en el Colegio de Agricultura y Artes Mecánicas de Mayaguez. De 1942 a 1946 sirvió como Oficial de Infantería del Ejército de los Estados Unidos en el Pacífico del Sur. Se graduó de Doctor en Medicina de la Universidad Central de Madrid, España en julio de 1952. Volvió a Puerto Rico en 1953 haciendo su internado y residencia en el Hospital Dr. Susoni de Arecibo, Puerto Rico. Cursó estudios post-graduados en la especialidad de Oftalmología en la Universidad de Pennsylvania durante 1957-59.



DR. MARTIN A. IGUINA MORA
Presidente, Asociación Médica de Puerto Rico
1969

Es miembro de la Cámara de Delegados de la Asociación Médica desde 1957. En 1965 ocupó la Presidencia de la Sociedad Médica del Distrito Norte y en 1966 y 1967 fue electo Secretario de la Asociación Médica.

Insomnia

Q Many of my patients, especially women, complain of difficulty in falling asleep and request quite persistently that I prescribe a "pill" for them. I am always somewhat reluctant to do this, but usually end off feeling it is best to let them get some sleep. But I feel rather guilty of rationalization. What is the best approach to this problem?

MD, San Juan

A The type of insomnia referred to is usually of a functional nature and occurs most frequently in those people whose daytime activities leaves them with a sense of incomplete fulfillment creating a state of tension or frustration. Women whose daily efforts with the children, the house cleaning, washing and a dozen other activities are not appreciated by their husbands, enter into a state of resentment that keeps them from falling asleep. Men whose efforts are not appreciated at their jobs or at home may have trouble falling asleep. Sexual maladjustment or guilt of infidelity may also be a cause.

It is unwise to prescribe hypnotics for these patients without first trying to unravel the contributive factor.

Experts on insomnia recommend the following before resorting to drugs:

1. Eliminate all stimulants like tea or coffee or other drinks containing coffeine at least six hours before contemplated bedtime.
2. Early light supper.
3. Light bland snack, like warm milk and crackers or bread just before bedtime.
4. Some physical exertion during the daytime. This should be avoided too near bedtime since exercise is a general physical and mental stimulant.
5. Warm bath just before bedtime.
6. The hour before bedtime should be spent quietly in some pleasant activity, like reading something light, listening to good music, or watching an amusing television program.
7. An alcoholic drink before bedtime as recommended by some, may help sleep but may also create dependence.

These measures are discussed with the patient and if the patient can make the necessary adjustment, it will be found that not only is the difficulty in falling asleep gradually eliminated, but the readjustment in the patient's routine will actually make him a happier individual.

Many patients actually fear that not being able to fall asleep easily will cause irreparable physical damage. They must be reassured that this is not necessarily so.

It is a great injustice to habituate this type of person with benign insomnia to hypnotics in an effort to solve the

immediate problem, and then to allow the perpertrative cause to go unchallenged. Yet most of us do just this in seeking the easier way out. Hypnotics usually are justified only during convalescence from an exhaustive illness or surgery.

Obesity

Q *What is the attitude of the Puerto Rico Medical Association towards general practitioners treating patients for obesity?*

MD, Río Piedras

A The present day emphasis on the hazards of excessive weight and the compulsion, especially amongst women, to remain slender and stylish, makes treatment of obesity a very lucrative financial enterprise indeed. This opens the way for the "obesity specialist", all too often an individual, somewhat unscrupulous, who builds up a large practice by giving appetite suppressors, diuretics, special diets and secret varicolored pills. Time does not allow him to give each patient the proper medical work-up and follow-up care, and treatment degenerates into a few verbal exchanges and a scale reading.

The ethical physician who wishes to devote himself to weight control problems exclusively, will thoroughly evaluate each case medically and follow each patient carefully.

Since overweight usually involves overeating and overeating is usually compulsive, the ideal physician to treat the usual overweight patient is the one who knows the patient and the family and with whom the patient is on easy emotional terms, and that would be the family physician.

Should the overweight problem involve endocrine imbalance, then an endocrinologist should naturally be consulted.

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Warning: In renal impairment, since liver toxicity is possible, lower doses are indicated; during prolonged therapy consider serum level determinations. Photodynamic reaction to sunlight may occur in hypersensitive persons. Photosensitive individuals should avoid exposure; discontinue treatment if skin discomfort occurs.

Precautions: Drowsiness, anorexia, slight gastric distress can occur. In excessive drowsiness, consider longer dosage intervals. Persons on full dosage should not operate vehicles. Nonsusceptible organisms may overgrow; treat superinfection appropriately. Treat beta-hemolytic streptococcal infections at least 10 days to help prevent rheumatic fever or acute glomerulonephritis. Tetracycline may form a stable calcium complex in bone-forming tissue and may cause dental staining during tooth development (last half of pregnancy, neonatal period, infancy, early childhood).

Adverse Reactions: *Gastrointestinal*—anorexia, nausea, vomiting, diarrhea, stomatitis, glossitis, enterocolitis, pruritus ani. *Skin*—maculopapular and erythematous rashes; exfoliative dermatitis; photosensitivity; onycholysis, nail discoloration. *Kidney*—dose-related rise in BUN. *Hypersensitivity* reactions—urticaria, angioneurotic edema, anaphylaxis. *Intracranial*—bulging fontanels in young infants. *Teeth*—yellow-brown staining; enamel hypoplasia. *Blood*—anemia, thrombocytopenic purpura, neutropenia, eosinophilia. *Liver*—cholestasis at high dosage.

Upon adverse reaction, stop medication and treat appropriately.

Lederle

350-8



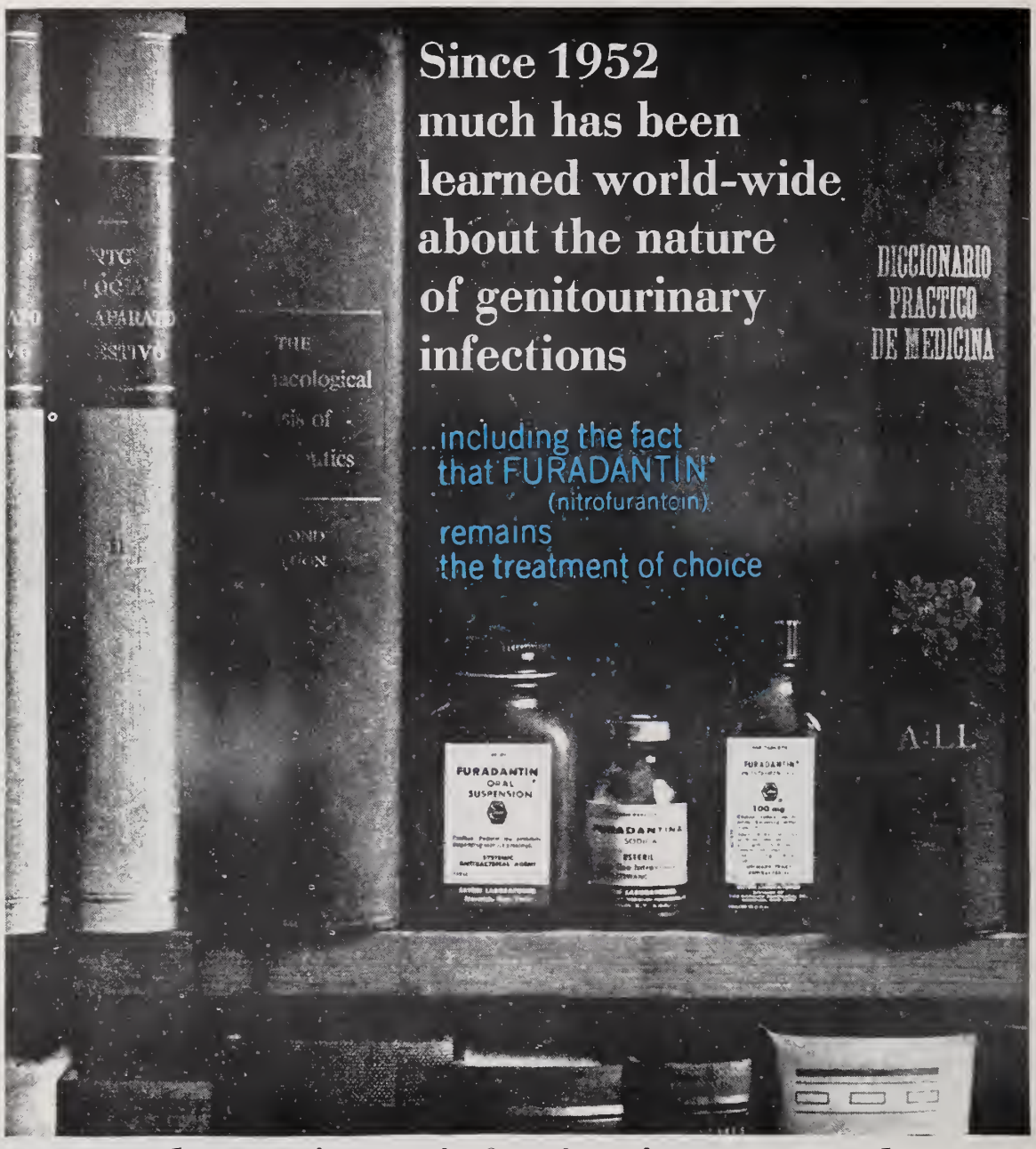
Lets you fit the formula to the infant

Carnation Evaporated Milk is not a rigid, ready-made infant formula. ▪ You choose the kind and amount of carbohydrate to be added. ▪ You specify the dilution with water. ▪ You maintain the right to prescribe the vitamin preparation of your choice. ▪ And you make the decision whether supplemental iron is needed. ▪ You fit the formula to the infant.

Millions of babies have benefited from *flexible, nutritious, economical* Carnation Evaporated Milk formulas . . . a tradition in infant feeding.

Specify Carnation Evaporated Milk and you specify Carnation quality.

From a world leader in nutritional research . . . Carnation®



when urinary infection is suspected,

try Furadantin first

· specific · safe · superior

Furadantin is supplied as Tablets, 50 mg. and 100 mg., bottles of 25, 100, 500 and 1000; and as Oral Suspension, bottles of 60 cc.

EATON LABORATORIES
Division of The Norwich Pharmacal Co., Norwich, New York, U.S.A.

Eaton*

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Otro nuevo descubrimiento de Lakeside



cuando la depresión abruma

NORPRAMIN
(clorhidrato de desipramina)

el ANTIDEPRESIVO
no-sedante de acción rápida

vence el abatimiento, levanta el ánimo, restablece la confianza

La depresión frecuentemente se caracteriza por sentimientos de culpabilidad, inutilidad, desolación y privación. Estas manifestaciones, acompañadas de síntomas tales como insomnio, malestar, tristeza y recelo, responden rápidamente al NORPRAMIN (clorhidrato de desipramina). La mejoría generalmente se manifiesta 2 a 5 días después de iniciado el tratamiento; algunas veces antes. Los pacientes con sensibilidad comprobada a estimulantes del sistema nervioso central, pueden experimentar excitación al desaparecer su depresión; en estos casos se sugiere reducir la dosis o administrar simultáneamente tranquilizantes.

Indicaciones: Depresiones de todo tipo, reacciones depresivas neuróticas o psicóticas; reacciones maniaco-depresivas o involucionales.

Posología: Se obtienen resultados óptimos con una dosis de 150 mg. diarios.

Contraindicaciones y Precauciones: Glaucoma, espasmo uretral o ureteral, infarto reciente del miocardio, trastornos cardiacos coronarios graves y epilepsia. No deberá administrarse durante las dos semanas subsiguientes a la suspensión de la terapia con inhibidores de monoamino-oxidasa. La seguridad de su empleo en el embarazo no ha sido aún establecida.

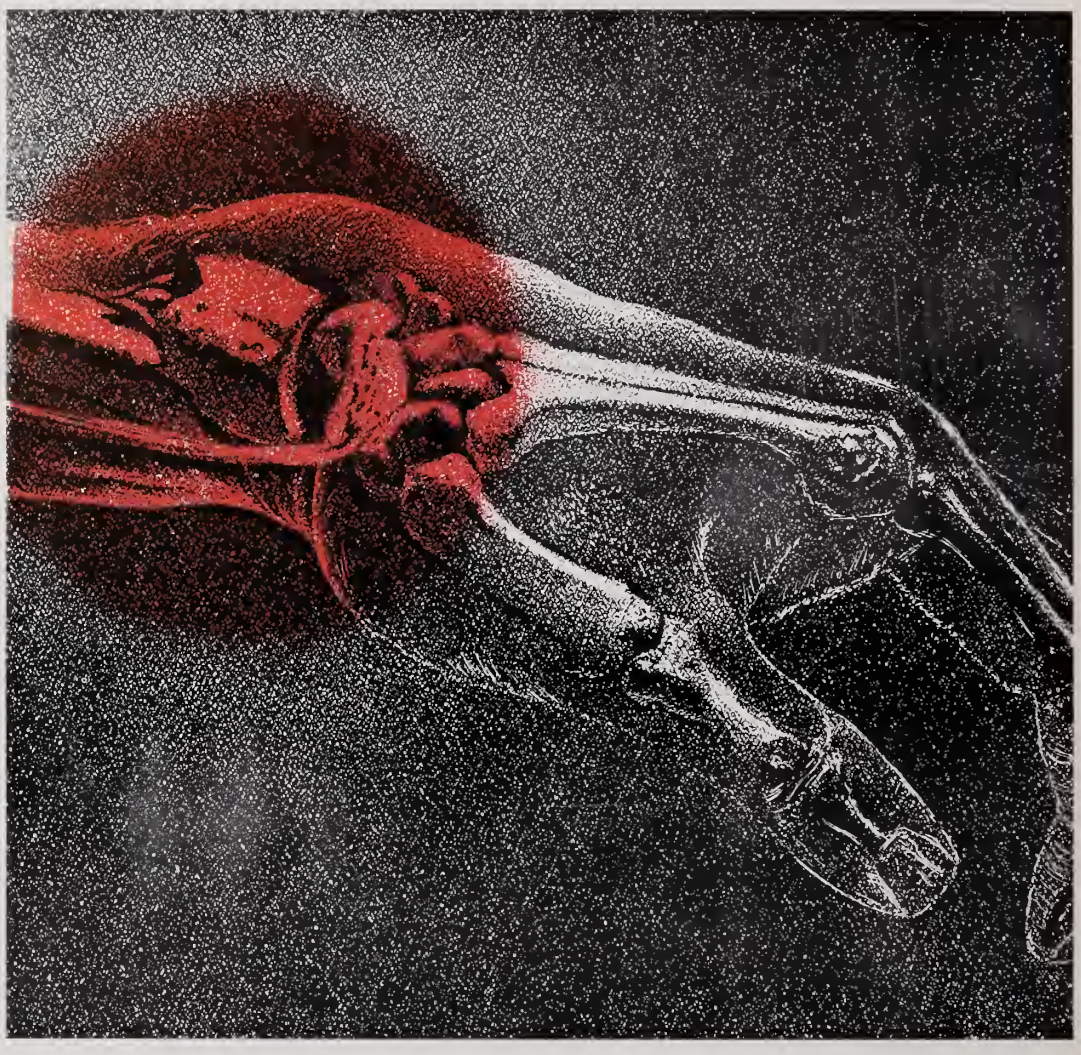
Reacciones Adversas: Pueden presentarse los siguientes efectos secundarios, generalmente leves: sequedad de boca, estreñimiento, mareo, palpitación, micción retardada "mal sabor", ilusiones sensorias, tinnitus, agitación y estimulación, sudoración, somnolencia, jaqueca, hipotensión ortostática, rubor, náusea, calambres, debilidad, visión borrosa y midriasis, salpullido, alergia, eosinofilia transitoria, granulopenia, alteraciones de la función hepática y signos extraoiramidales.

Presentación: NORPRAMIN (Clorhidrato de desipramina)—tabletas de 25 mg. en frascos de 50, 500 y 1000. Tabletas de 50 mg. en frascos de 30, 250 y 1000.

LAKESIDE

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PARA PACIENTES
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Lakeside Laboratories, Inc. Milwaukee, Wisconsin 53201—EE.UU.



Can fracture cases do better with Ananase?

This one did: A 42-year-old fireman fell and suffered a fracture of his left wrist. When pressure and edema appeared to be increasing under the cast, Ananase was used adjunctively for a trial period of 24 hours. "When seen the next morning, all edema and pressure had disappeared." Marked relief was experienced with no further treatment.[1]

When the effect of Ananase on inflammation and edema was compared with the expected response to conventional therapy, without Ananase, "superior" results were obtained with Ananase in 83% of 18 fracture cases observed.[1]

Your own experience will confirm the efficacy of Ananase in helping to reduce inflammation and edema and speeding the healing process. For best results give Ananase early and in maximum dosage.

Usual Adult Dose: Initially, two tablets four times daily. For maintenance, one tablet three or four times daily.

Side Effects: Ananase has a wide margin of safety. There have been few toxic effects reported. It should be used with caution in patients with abnormalities of the blood clotting mechanism, such as hemophilia, or with severe hepatic or renal disease.

Supplied: Bottles of 100 and 500 tablets, each tablet containing 50,000 Rorer units.

One Rorer unit of protease activity is defined as that amount of enzyme which will so hydrolyze a standardized casein substrate at pH 7.0 and 25° C temperature as to cause a change in absorbance of 1×10^{-5} at 280 mu per minute of reaction time.

1. Cirelli, M. G.: Delaware M. J. *34*:159 (June) 1962.

ROHER

WILLIAM H. RORER, INC.
FORT WASHINGTON, PA.

Ananase®
(plant protease concentrate)



para esa tos molesta recomiende el nuevo jarabe, sin narcóticos

Cheracol D

dominio efectivo de la tos, sin codeína

Cheracol D con dextrometorfano:

- acción antitusiva igual que con codeína, pero sin efectos secundarios narcóticos indeseables
- afloja las secreciones bronquiales
- refresca y suaviza la garganta
- tiene un agradable sabor a cerezas que lo hace muy popular entre los niños
- puede ser administrado a niños menores de dos años, bajo la vigilancia del médico

Cada onza fluida contiene:	
Bromhidrato de dextrometorfano	9/10 gr. (60 mg.)
Cloroformo*	2 grs.
Guayacolato de Glicerilo	1⅔ grs.
Cloruro de Amonio	8 grs.
Tartrato de Antimonio y Potasio	1/12 gr.
Alcohol	3%

con corteza de pino blanco y de cerezo silvestre
*Cierta pérdida de cloroformo es inevitable.

Presentación: en frascos de 2 y 4 onzas.

Upjohn

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...because psychic tension may not stop at night

The calming action of Valium (diazepam) helps counteract psychic tension and reduce overreaction to stresses during the day. Often the t.i.d. dosage schedule is enough to prevent build-up of tenseness that may interfere with sleep at night.

However, when psychic tension does contribute to sleeplessness, Valium can be especially useful. A tablet at bedtime, added to the daytime t.i.d. dosage, can help your patient be ready for bed *and* for sleep.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms have occurred following abrupt discontinuance. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation, have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Valium®
(diazepam)

ROCHE

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LABORATORIES

Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

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